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(54) Title: RECOMBINANT PROTEIN PRODUCTION IN BOVINE ADENOVIRUS EXPRESSION VECTOR SYSTEM

(57) Abstract

The present invention relates to novel live bovine adenovirus (BAV) expression vector systems in which part or all of one or both of the early region 1 (E1) and early region 3 (E3) genes are deleted and replaced by a foreign gene or fragment thereof and novel recombinant mammalian cell lines stably transformed with BAV E1 sequences, and therefore, express E1 gene products capable of allowing replication therein of a bovine adenovirus having an E1 deletion replaced by a heterologous nucleotide sequence encoding a foreign gene or fragment thereof and their use in production of (antigenic) polypeptides or fragments thereof for the purpose of live recombinant virus or subunit vaccine or for other therapies.

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RECOMBINANT PROTEIN PRODUCTION IN BOVINE ADENOVIRUS EXPRESSION VECTOR SYSTEM

Technical Field

The present invention relates novel bovine adenovirus (BAV) expression vector systems in which one or both of the early region 1 (E1) and the early region 3 (E3) gene deletions are replaced by a foreign gene and novel recombinant mammalian cell lines stably transformed with BAV E1 sequences, and therefore, expresses E1 gene products, to allow a bovine adenovirus with an E1 gene deletion replaced by a foreign gene to replicate therein. These materials are used in production of recombinant BAV expressing heterologous (antigenic) polypeptides or fragments for the purpose of live recombinant virus or subunit vaccines or for other therapies.

Background of the Invention

The adenoviruses cause enteric or respiratory infection in humans as well as in domestic and laboratory animals.

The bovine adenoviruses (BAVs) comprise at least nine serotypes divided into two subgroups. These subgroups have been characterized based on enzyme-linked immunoassays (ELISA), serologic studies with immunofluorescence assays, virus-neutralization tests, immunoelectron microscopy, by their host specificity and clinical syndromes. Subgroup 1 viruses include BAV 1, 2, 3 and 9 and grow relatively well in established bovine cells compared to subgroup 2 which includes BAV 4, 5, 6, 7 and 8.

BAV3 was first isolated in 1965 and is the best characterized of the BAV genotypes and contains a

genome of approximately 35 kb (Kurokawa et al (1978) J. Virol. 28:212-218). The locations of hexon (Hu et al (1984) J. Viol. 49:604-608) and proteinase (Cai et al., (1990) Nuc. Acids Res., 18:5568), genes in the BAV3 genome have been identified and sequenced. However, the location and sequences of other genes such as early region 1 (E1) and 3 (E3) in the BAV genome have not been reported.

In the human adenovirus (HAd) genome there are two important regions: E1 and E3 in which foreign genes can be inserted to generate recombinant adenoviruses (Berkner and Sharp (1984) Nuc. Acid Res., 12:1925-1941 and Haj-Ahmad and Graham (1986) J. Virol., 57:267-274). E1 proteins are essential for virus replication in tissue culture, however, conditional-helper adenovirus recombinants containing foreign DNA in the E1 region, can be generated in a cell line which constitutively expresses E1 (Graham et al., (1977) J. Gen. Virol., 36:59-72). In contrast, E3 gene products of HAd 2 and HAd 5 are not required for in vitro or in vivo infectious virion production, but have an important role in host immune responses to virus infection (Andersson et al (1985) Cell 43:215-222; Burgert et al (1987) EMBO J. 6:2019-2026; Carlin et al (1989) Cell 57:135-144; Ginsberg et al (1989) PNAS, USA 86:3823-3827; Gooding et al (1988) Cell 53:341-346; Tollefson et al (1991) J. Virol. 65:3095-3105; Wold and Gooding (1989) Mol. Biol. Med. 6:433-452 and Wold and Gooding (1991) Virology 184:1-8). The E3-19kiloDalton (kDa) glycoprotein (gp19) of human adenovirus type 2 (HAd2) binds to the heavy chain of a number of class 1 major histocompatibility complex (MHC) antigens in the endoplasmic reticulum thus inhibiting their transport to the plasma membrane (Andersson et al. (1985) Cell 43:215-222; Burgert and Kvist, (1985) Cell 41:987-997; Burgert and Kvist, (1987) EMBO J. 6:2019-2026). The E3-14.7kDa protein of HAd2 or HAd5 prevents lysis of virus-infected mouse cells by tumor necrosis factor (TNF) (Gooding et al.

(1988) Cell 53:341-346). In addition, the E3-10.4kDa and E3-14.5kDa proteins form a complex to induce endosomal-mediated internalization and degradation of the epidermal growth factor receptor (EGF-R) in virus-infected cells (Carlin et al. Cell 57:135-144; Tollefson et al. (1991) J. Virol. 65:3095-3105). The helper-independent recombinant adenoviruses having foreign genes in the E3 region replicate and express very well in every permissive cell line (Chanda et al (1990) Virology 175:535-547; Dewar et al (1989) J. Virol. 63:129-136; Johnson et al (1988) Virology 164:1-14; Lubeck et al (1989) PNAS, USA 86:6763-6767; McDermott et al (1989) Virology 169:244-247; Mittal et al (1993) Virus Res. 28:67-90; Morin et al (1987) PNAS, USA 84:4626-4630; Prevec et al (1990) J. Inf. Dis. 161:27-30; Prevec et al (1989) J. Gen. Virol. 70:429-434; Schneider et al (1989) J. Gen. Virol. 70:417-427 and Yuasa et al (1991) J. Gen. Virol. 72:1927-1934). Based on the above studies and the suggestion that adenoviruses can package approximately 105% of the wild-type (wt) adenovirus genome (Bett et al (1993) J. Virol. 67:5911-5921 and Ghosh-Choudhury et al (1987) EMBO. J. 6:1733-1739), an insertion of up to 1.8 kb foreign DNA can be packaged into adenovirus particles for use as an expression vector for foreign proteins without any compensating deletion.

It is assumed that an indigenous adenovirus vector would be better suited for use as a live recombinant virus vaccine in different animal species compared to an adenovirus of human origin. Non-human adenovirus-based expression vectors have not been reported so far. If like HAds E3, the E3 regions in other adenoviruses are not essential for virus replication in cultured cells, adenovirus recombinants containing foreign gene inserts in the E3 region could be generated.

BAV3 is a common pathogen of cattle usually resulting in subclinical infection though occasionally associated with a more serious respiratory tract

infection (Darbyshire et al., 1966 Res. Vet Sci 7:81-93; Mattson et al., 1988 J. Vet Res 49:67-69). BAV3 can produce tumors when injected into hamsters (Darbyshire, 1966 Nature 211:102) and viral DNA can efficiently effect morphological transformation of mouse, hamster or rat cells in culture (Tsukamoto and Sugino, 1972 J. Virol. 9:465-473; Motoi et al., 1972 Gann 63:415-418; M. Hitt, personal communication). Cross hybridization was observed between BAV3 and human adenovirus type 2 (HAd2) (Hu et al., 1984 J. Virol. 49:604-608) in most regions of the genome including some regions near but not at the left end of the genome.

The E1A gene products of the group C human adenoviruses have been very extensively studied and shown to mediate transactivation of both viral and cellular genes (Berk et al., 1979 Cell 17:935-944; Jones and Shenk, 1979 Cell 16:683-689; Nevins, 1981 Cell 26:213-220; Nevins, 1982 Cell 29:913-919; reviewed in Berk, 1986 Ann. Res. Genet 20:45-79), to effect transformation of cells in culture (reviewed in Graham, F.L. (1984) "Transformation by and oncogenicity of human adenoviruses. In:The Adenoviruses." H.S. Ginsberg, Editor. Plenum Press, New York; Branton et al., 1985 Biochim. Biophys. Acta 780:67-94) and induce cell DNA synthesis and mitosis (Zerler et al., 1987 Mol. Cell Biol. 7:821-929; Bellet et al., 1989 J. Virol. 63:303-310; Howe et al., 1990 PNAS, USA 87:5883-5887; Howe and Bayley, 1992 Virology 186:15-24). The E1A transcription unit comprises two coding sequences separated by an intron region which is deleted from all processed E1A transcripts. In the two largest mRNA species produced from the E1A transcription unit, the first coding regions is further subdivided into exon 1, a sequence found in both the 12s and 13s mRNA species, and the unique region, which is found only in the 13s mRNA species. By

comparisons between E1A proteins of human and simian adenoviruses three regions of somewhat conserved protein sequence (CR) have been defined (Kimelman et al., 1985 J. Virol. 53:399-409). CR1 and CR2 are encoded in exon 1, while CR3 is encoded in the unique sequence and a small portion of exon 2. Binding sites for a number of cellular proteins including the retinoblastoma protein Rb, cyclin A and an associated protein kinase $p33^{cdk2}$, and other, as yet unassigned, proteins have been defined in exon 1 encoded regions of E1A proteins (Yee and Branton, 1985 Virology 147:142-153; Harlow et al., 1986 Mol. Cell Biol. 6:1579-1589; Barbeau et al., 1992 Biochem. Cell Biol. 70:1123-1134). Interaction of E1A with these cellular proteins has been implicated as the mechanism through which E1A participates in immortalization and oncogenic transformation (Egan et al, 1989 Oncogene 4:383-388; Whyte et al., 1988 Nature 334:124-129; Whyte et al, 1988 J. Virol. 62:257-265). While E1A alone may transform or immortalize cells in culture, the coexpression of both E1A and either the E1B-19k protein or the E1B-55k protein separately or together is usually required for high frequency transformation of rodent cells in culture (reviewed in Graham, 1984 supra; Branton et al., 1985 supra; McLorie et al., 1991 J. Gen Virol. 72:1467-1471).

Transactivation of other viral early genes in permissive infection of human cells is principally mediated by the amino acid sequence encoded in the CR3 region of E1A (Lillie et al., 1986 Cell 46:1043-1051). Conserved cysteine residues in a $CysX_2CysX_{13}CysX_2Cys$ sequence motif in the unique region are associated with metal ion binding activity (Berg, 1986 supra) and are essential for transactivation activity (Jelsma et al., 1988 Virology 163:494-502; Culp et al., 1988 PNAS, USA 85:6450-6454). As well, the amino acids in CR3 which are immediately amino (N)-terminal to the metal binding domain have been shown to be important

in transcription activation, while those immediately carboxy (C)-terminal to the metal binding domain are important in forming associations with the promoter region (Lillie and Green, 1989 Nature 338:39-44; see Fig. 3).

The application of genetic engineering has resulted in several attempts to prepare adenovirus expression systems for obtaining vaccines. Examples of such research include the disclosures in U.S. patent 4,510,245 on an adenovirus major late promoter for expression in a yeast host; U.S. patent 4,920,209 on a live recombinant adenovirus type 7 with a gene coding for hepatitis-B surface antigen located at a deleted early region 3; European patent 389 286 on a non-defective human adenovirus 5 recombinant expression system in human cells for HCMV major envelope glycoprotein; WO 91/11525 on live non-pathogenic immunogenic viable canine adenovirus in a cell expressing E1a proteins; French patent 2 642 767 on vectors containing a leader and/or promoter from the E3 of adenovirus 2.

The selection of a suitable virus to act as a vector for foreign gene expression, and the identification of a suitable non-essential region as a site for insertion of the gene pose a challenge. In particular, the insertion site must be non-essential for the viable replication of the virus and its effective operation in tissue culture and also in vivo. Moreover, the insertion site must be capable of accepting new genetic material, whilst ensuring that the virus continues to replicate. An essential region of a virus genome can also be utilized for foreign gene insertion if the recombinant virus is grown in a cell line which complements the function of that particular essential region in trans.

The present inventors have now identified suitable regions in the BAV genome and have succeeded in inserting foreign genes to generate BAV recombinants.

Disclosure of the Invention

The present invention relates to novel bovine adenovirus expression vector systems in which part or all of one or both of the E1 and E3 gene regions are deleted and to recombinant mammalian cell lines of bovine origin transformed with the BAV E1 sequences, and thus, constitutively express the E1 gene products to allow bovine adenovirus, having a deletion of part or all of the E1 gene region replaced by a heterologous nucleotide sequence encoding a foreign gene or fragment thereof, to replicate therein and use of these materials in production of heterologous (antigenic) polypeptides or fragments thereof.

The invention also related to a method of preparing a live recombinant virus or subunit vaccines for producing antibodies or cell mediated immunity to an infectious organism in a mammal, such as bovine, which comprises inserting into the bovine adenovirus genome the gene or fragment coding for the antigen which corresponds to said antibodies or induces said cell mediated immunity, together with or without an effective promoter therefore, to produce BAV recombinants.

Generally, the foreign gene construct is cloned into a nucleotide sequence which represents only a part of the entire viral genome having one or more appropriate deletions. This chimeric DNA sequence is usually present in a plasmid which allows successful cloning to produce many copies of the sequence. The cloned foreign gene construct can then be included in the complete viral genome, for example, by in vivo recombination following a DNA-mediated cotransfection technique. Multiple copies of a coding sequence or more than one coding sequences can be inserted so that the recombinant vector can express more than one foreign protein. The foreign gene can have additions, deletions or substitutions to enhance

expression and/or immunological effects of the expressed protein.

The invention also includes an expression system comprising an bovine adenovirus expression vector wherein heterologous nucleotide sequences with or without any exogenous regulatory elements, replace the E1 gene region and/or part or all of the E3 gene region.

The invention also includes (A) a recombinant vector system comprising the entire BAV DNA and a plasmid or two plasmids capable of generating a recombinant virus by in vivo recombination following cotransfection of a suitable cell line comprising BAV DNA representing the entire wild-type BAV genome and a plasmid comprising a bovine adenovirus left or right end sequences containing the E1 or E3 gene regions, respectively, with a heterologous nucleotide sequence encoding a foreign gene or fragment thereof substituted for part or all of the E1 or E3 gene regions; (B) a live recombinant bovine adenovirus vector (BAV) system selected from the group consisting of: (a) a system wherein part or all of the E1 gene region is replaced by a heterologous nucleotide sequence encoding a foreign gene or fragment thereof; (b) a system wherein a part or all of the E3 gene region is replaced by a heterologous nucleotide sequence encoding a foreign gene or fragment thereof; and (c) a system wherein part or all of the E1 gene region and part or all of the E3 gene region are deleted and a heterologous nucleotide sequence encoding a foreign gene or fragment thereof is inserted into at least one of the deletions; (C) a recombinant bovine adenovirus (BAV) comprising a deletion of part or all of E1 gene region, a deletion of part or all of E3 gene region or deletion of both, and inserted into at least one deletion a heterologous nucleotide sequence coding for an antigenic determinant of a disease causing organism; (D) a recombinant bovine adenovirus

expression system comprising a deletion of part or all of E1, a deletion of part or all of E3, or both deletions, and inserted into at least one deletion a heterologous nucleotide sequence coding for a foreign gene or fragment thereof under control of an expression promoter: or (E) a recombinant bovine adenovirus (BAV) for producing an immune response in a mammalian host comprising: (1) BAV recombinant containing a heterologous nucleotide sequence coding for an antigenic determinant needed to obtain the desired immune response in association with or without (2) an effective promoter to provide expression of said antigenic determinant in immunogenic quantities for use as a live recombinant virus or recombinant protein or subunit vaccine; (F) a mutant bovine adenovirus (BAV) comprising a deletion of part or all of E1 and/or a deletion of part or all of E3.

Recombinant mammalian cell lines stably transformed with BAV E1 gene region sequences, said recombinant cell lines thereby capable of allowing replication therein of a bovine adenovirus comprising a deletion of part or all of the E1 or E3 gene regions replaced by a heterologous or homologous nucleotide sequence encoding a foreign gene or fragment thereof. The invention also includes production, isolation and purification of polypeptides or fragments thereof, such as growth factors, receptors and other cellular proteins from recombinant bovine cell lines expressing BAV E1 gene products.

The invention also includes a method for providing gene therapy to a mammal in need thereof to control a gene deficiency which comprises administering to said mammal a live recombinant bovine adenovirus containing a foreign nucleotide sequence encoding a non-defective form of said gene under conditions wherein the recombinant virus vector genome is incorporated into said mammalian genome or is maintained independently and extrachromosomally to

provide expression of the required gene in a target organ or tissue.

Another aspect of the invention provides a virus vaccine composition which comprises the recombinant virus or recombinant protein in association with or without a pharmaceutically acceptable carrier. The recombinant virus vaccine can be formulated for administration by an oral dosage (e.g. as an enteric coated tablet), by injection or otherwise. More specifically, these include a vaccine for protecting a mammalian host against infection comprising a live recombinant adenovirus or recombinant protein produced by the recombinant adenovirus of the invention wherein the foreign gene or fragment encodes an antigen and formulated with or without a pharmaceutically acceptable carrier.

The invention also includes methods of producing antibodies or cell mediated immunity in a mammal including (1) a method for eliciting an immune response in a mammalian host against an infection comprising: administering a vaccine comprising a live BAV recombinant of the invention wherein the foreign gene or fragment encodes an antigen with or without a pharmaceutically acceptable carrier, and (2) a method for eliciting an immune response in a mammalian host against an infection comprising: administering a vaccine comprising a recombinant antigen prepared by culturing a BAV recombinant wherein the foreign gene or fragment encodes the desired antigen with or without a pharmaceutically acceptable carrier.

The following disclosure will render these and other embodiments of the present invention readily apparent to those of skill in the art. While the disclosure often refers to bovine adenovirus type 3 (BAV3), it should be understood that this is for the purpose of illustration and that the same features apply to bovine adenovirus of the other type, 1, 2, 4, 5, 6, 7 8, and 9 and the invention described and

claimed herein is intended to cover all of these bovine adenovirus types.

Brief Description of the Drawings

Figure 1. Sequence and major open reading frames of the left 11% of the BAV3 genome. The region comprises the E1 and protein IX transcription region. The 195 nucleotide inverted terminal repeat sequence identified by Shinagawa et al., 1987 Gene 55:85-93 is shown in *italics*. The amino acid sequence for the largest E1A protein, two E1B proteins and protein IX are presented. The probable splice donor ([), splice acceptor (]) and intron sequence (*underlined italics*) within the E1A region are marked. A 35 base pair repeat sequence between E1A and E1B is indicated in **bold underline**. Possible transcription promoter **TATA** sequences and possible poly A addition sequences **AATAA** are also indicated.

Figure 2. Regions of homology in the E1A proteins of BAV3 and human adenovirus type 5 (HAd5). The amino acid residue of each serotype is indicated. A. Conserved region 3 (CR3) of HAd5 subdivided into three functional regions as defined by Lillie et al (1989) Nature 338:39-44 and described in the Background of the Invention. The intron sequence of BAV3 E1A occurs within the serine amino acid codon at position 204. B. A portion of conserved region 2 (CR2) of HAd5, showing the residues thought to be important in the binding of retinoblastoma protein Rb (Dyson et al., 1990 J. Virol. 64:1353-1356), and the comparable sequence from BAV3.

Figure 3. Homology regions between the HAd5 and E1B 19k (176R) protein and the corresponding BAV3 (157R) protein. The amino acid residue number for each of the viruses is indicated.

Figure 4. The C-terminal 346R of HAd5 E1B 56k (496R) and the corresponding BAV3 protein (420R). The HAd5 protein comparison begins at residue 150 and the BAV3 (in italics) at residue 74.

The amino terminal regions of these proteins which are not presented show no significant homology.

Figure 5. Homology comparison of the amino acid sequence of HAd5 protein IX and the corresponding protein of BAV3 (in italics).

Figure 6. The genome of BAV3 showing the location of *Eco*RI, *Xba*I and *BAM*HI sites and the structure of the 5100bp segment from 77 to 92 m.u. ORFs for the upper strand which can encode 60 amino acids or more are represented by bars. Shaded portions indicate regions of similarity to pVIII, 14.7K E3 and fibre proteins of HAd2 or -5. The first methionine followed by a stretch of amino acids of at least 50 is shown by an open triangle. Termination codons for ORFs likely to code for viral proteins are shown by closed triangles.

Figure 7. Nucleotide sequence of BAV3 between 77 and 92 m.u. showing ORFs that have the potential to encode polypeptides of at least 50 amino acids after the initiating methionine. The nucleotide sequence was analyzed using the program DISPCOD (PC/GENE). Potential N-glycosylation sites (N-X-T/S) and polyadenylation signals are underlined and the first methionine of each ORF is shown in bold.

Figure 8. Comparison between the predicted amino acid sequences for the ORFs of BAV3 and known proteins of HAd2 or -5 using the computer program PALIGN (PC/GENE), with comparison matrix structural-genetic matrix; open gap cost 6; unit gap cost 2. Identical residues are indicated by a colon and similar residues by a dot. (a) Comparison between the predicted amino acid sequence encoded by the 3′ end of BAV3 ORF 1 and the HAd2 hexon-associated pVIII precursor. (b) Comparison between the ORF 4 and the HAd5 14.7K E3 protein. (c) Comparison between the predicted amino acid sequence encoded by BAV3 ORF 6 and the HAd2 fibre protein.

Figure 9. Construction of BAV3 E3 transfer vector containing the firefly luciferase gene. The

3.0 kb BamHI 'D' fragment of the BAV3 genome which falls between m.u. 77.8 and 86.4, contains almost the entire E3 region (Mittal et al (1992) J. Gen. Virol. 73:3295-3000). This 3.0 kb fragment was isolated by digesting BAV3 DNA with BamHI and cloned into pUC18 at the BamHI site to obtain pSM14. Similarly, the 4.8 kb BamHI 'C' fragment of BAV3 DNA which extends between m.u. 86.4 and 100 was isolated and inserted into pUC18 to produce pSM17. To delete a 696 bp XhoI-NcoI fragment, pSM14 was cleaved with XhoI and NcoI, the larger fragment was purified and the ends were made blunt with Klenow fragment of DNA polymerase I and a NruI-SalI linker was inserted to generate pSM14de12. A 2.3 kb BamHI fragment containing BAV3 sequences, an E3 deletion and NruI and SalI cloning sites, was inserted into pSM17 at the BamHI site to obtain pSM41, however, this step was not required for construction of a BAV3 E3 transfer vector. A 1716 bp fragment containing the firefly luciferase gene (de Wet et al (1987) Mol. Cell. Biol. 7:725-737) was isolated by digesting pSVOA/L (provided by D. R. Helinski, University of California at San Diego, CA) with BsmI and SspI as described (Mittal et al (1993) Virus Res. 28:67-90), and the ends were made blunt with Klenow. The luciferase gene was inserted into pSM41 at the SalI site by blunt end ligation. The resultant plasmid was named pSM41-Luc which contained the luciferase gene in the same orientation as the E3 transcription unit. The plasmid pKN30 was digested with XbaI and inserted into pSM41-Luc (partially cleaved with XbaI) at a XbaI site present within the luciferase gene to obtain pSM41-Luc-Kan. The plasmid pSM14 was digested with BamHI and a 3.0 kb fragment was isolated and inserted into pSM17 at the BamHI site to generate pSM43. The 18.5 kb XbaI 'A' fragment of the BAV3 genome which falls between m.u. 31.5 and 84.3 was cloned into pUC18 at the XbaI site to result pSM21. A 18.5 kb XbaI fragment was purified from pSM21 after cleavage with XbaI and

inserted into pSM43 at the XbaI site and the resultant plasmid was named pSM51. A 7.7 kb BamHI fragment containing the luciferase gene and kan^r gene was isolated after digesting pSM41-Luc-Kan with BamHI and ligated to pSM51, partially digested with BamHI, to isolate pSM51-Luc-Kan in the presence of ampicillin and kanamycin. Finally the kan^r gene was deleted from pSM51-Luc-Kan by partial cleavage with XbaI and religation to obtain pSM51-Luc.

Figure 10. Generation of BAV3 recombinants containing the firefly luciferase in the E3 region. The plasmid pSM51-Luc contains the BAV3 genome between m.u. 77.8-84.3 and 31.5-100, a 696 bp deletion in E3 and the luciferase gene in E3 in the E3 parallel orientation. The BAV3 genome digested with PvuI and uncut pSM51-Luc were used for cotransfection of MDBK cells transformed with a plasmid containing BAV3 E1 sequences to rescue the luciferase gene in E3 of the BAV3 genome by *in vivo* recombination. The resulting BAV3-luciferase recombinants (BAV3-Luc) isolated from two independent experiments were named BAV3-Luc (3.1) and BAV3-Luc (3.2). The BamHI restriction map of the BAV3-Luc genome is shown. The position and orientation of the firefly luciferase gene is shown as a hatched arrow.

Figure 11. Southern blot analyses of restriction enzymes digested DNA fragments of the wt BAV3 or recombinant genomes by using a 696 bp XhoI-NcoI fragment from pSM14 (Fig. 9) and a DNA fragment containing the luciferase gene as probes. 100 ng DNA isolated from the mock (lanes 1, 2, 3), BAV3-Luc (3.1) (lanes 4, 5, 6), BAV3-Luc (3.2) (lanes 7, 8, 9) or wt BAV3 (lanes 10, 11 12)-infected MDBK cells were digested with BamHI (lanes 1, 4, 7, 10), EcoRI (lanes 2, 5, 8, 11) or XbaI (lanes 3, 6, 9, 12) and analyzed by agarose gel electrophoresis. The DNA fragments from the gel were transferred onto a *GeneScreenPlus*™ membrane and hybridized with a 696 bp XhoI-NcoI

fragment from pSM14 (Fig. 9) labeled with ^{32}P using Pharmacia Oligolabeling Kit (panel A). Panel B blot represents duplicate samples as in panel A but was probed with a 1716 bp BsmI-SspI fragment containing the luciferase gene (Fig. 9). The sizes of bands visualized following hybridization are shown in kb on the right in panel A and on the left in panel B.
B: BamHI, E: EcoRI, Xb: XbaI, 3.1: BAV3-Luc (3.1), 3.2: BAV3-Luc (3.2) and wt: wild-type BAV3.

Figure 12. Single step growth curve for wt BAV3 and BAV3-Luc. Confluent monolayers of MDBK cells in 25 mm multi-well culture plates were inoculated with the wt BAV3, BAV3-Luc (3.1) or BAV3-Luc (3.2) at a m.o.i. of 10 p.f.u. per cell. The virus was allowed to adsorb for 1 h at 37°C, cell monolayers were washed 3 times with PBS^{++} (0.137 M NaCl, 2.7 mM KCl, 8 mM Na_2HPO_4, 1.5 mM KH_2PO_4, containing 0.01% $CaCl_2.2H_2O$ & 0.01% $MgCl_2.6H_2O$) and incubated at 37°C in 1 ml maintenance medium containing 2% horse serum. At various times post-infection, cells were harvested along with the supernatant, frozen and thawed three times and titrated on MDBK cells by plaque assay. Results are the means of duplicate samples.

Figure 13. Kinetics of luciferase expression in MDBK cells-infected with BAV3-Luc. Confluent MDBK cell monolayers in 25 mm multi-well culture plates were infected with BAV3-Luc (3.1) or BAV3-Luc (3.2) at a m.o.i. of 50 p.f.u. per cell. At indicated time points post-infection, virus-infected cells were harvested and assayed in duplicate for luciferase activity.

Figure 14. Luciferase expression in the presence of 1-β-D-arabinofluranosyl cytosine (AraC) in MDBK cells-infected with BAV3-Luc. Confluent MDBK cell monolayers in 25 mm multi-well culture plates were infected with A) BAV3-Luc (3.1) or B) BAV3-Luc (3.2) at a m.o.i. of 50 p.f.u. per cell and incubated in the absence or presence of 50 μg AraC per ml of

maintenance medium. At indicated time points post-infection, virus-infected cells were harvested and assayed in duplicate for luciferase activity.

Figure 15. Transcription maps of the wt BAV3 and BAV3-Luc genomes in the E3 region. The genome of wt BAV3 between m.u. 77 and 82 is shown which represents the E3 region. The location of XhoI and NcoI sites which were used to make an E3 deletion are shown. (a) The three frames (F1, F2 and F3) representing the open reading frames (ORFs) in the upper strand of the wt BAV3 genome in the E3 region are represented by bars. The shaded portions indicate regions of similarities to pVIII and E3-14.7 kDa proteins of HAd5. The positions of the initiation and termination codons for ORFs likely to code for viral proteins are shown by open and closed triangles, respectively. (b) The predicted ORFs for the upper strand in E3 of the BAV3-Luc genome are shown after a 696 bp XhoI-NcoI E3 deletion replaced by the luciferase gene. The ORFs for pVIII and E3-14.7 kDa proteins are intact. The transcription map of the wt BAV3 E3 was adapted from the DNA sequence submitted to the GenBank database under accession number D16839.

Figure 16. Western blot analysis of virus-infected MDBK cells using an anti-luciferase antibody. Confluent monolayers of MDBK cells were mock-infected (lane 1) or infected with the wt BAV3 (lane 2), BAV3-Luc (3.1) (lane 3) and BAV3-Luc (3.2) (lane 4) at a m.o.i. of 50 p.f.u. per cell, harvested at 18 h post-infection, cell extracts prepared and analyzed by SDS-PAGE and Western blotting using a rabbit anti-luciferase antibody. Purified firefly luciferase was used as a positive control (lane 5). The lane 5 was excised to obtain a shorter exposure. The protein molecular weight markers in kDa are shown on the left. The arrow indicates the 62 kDa luciferase bands reacted with the anti-luciferase antibody.
wt: wild-type BAV3, 3.1: BAV3-Luc (3.1) and 3.2: BAV3-Luc (3.2).

Figure 17. Construction of pSM71-neo. A 8.4 kb SalI fragment of the BAV3 genome which falls between m.u. 0 and 24 was isolated and inserted into pUC19 at the SalI-SmaI site to generate pSM71. The plasmid, pRSDneo (Fitzpatrick et al (1990) Virology 176:145-157) contains the neomycin-resistant (neo^r gene flanked with the simian virus 40 (SV40) regulatory sequences originally from the plasmid, pSV2neo (Southern et al (1982) J. Mol. Appl. Genet 1:327-341) after deleting a portion of the SV40 sequences upstream of the neo^r gene to remove several false initiation codons. A 2.6 kb fragment containing the neo^r gene under the control of the SV40 regulatory sequences, was obtained from the plasmid, pRSDneo after digestion with BamHI and Bg1II, and cloned into pSM71 at the SalI site by blunt end ligation to obtain pSM71-neo containing the neo^r gene in the E1 parallel orientation.

Figure 18. Construction of pSM61-kan 1 and pSM61-kan2. A 11.9 kb Bg1II fragment of the BAV3 genome which extends between m.u. 0 and 34 was purified and introduced into pUC19 at the BamHI-HincII site to obtain pSM61. The plasmid, pKN30 contains the neo^r gene along with SV40 promoter and polyadenylation sequences from the plasmid pSV2neo without any modification. The entire pKN30 plasmid was inserted into pSM61 at the SalI site to generate pSM61-kan1 having the neo^r gene in the E1 anti-parallel orientation and pSM61-kan2 when the neo^r gene is in the E1 parallel orientation.

Figure 19. Construction of an E1 transfer plasmid containing the beta-galactosidase gene.

The plasmid, pSM71 which contains the BAV3 genome between m.u. 0 and 24, was cleaved with ClaI and partially with AvrII to delete a 2.6 kb AvrII-ClaI fragment (between m.u. 1.3 and 8.7) which falls within the E1 region. A 0.5 kb fragment containing the SV40 promoter and polyadenylation sequences was obtained

from pFG144K5-SV by digesting with XbaI and inserted into pSM71 to replace the 2.6 kb deletion to generate pSM71-del1-SV. A 3.26 kb fragment containing the bacterial beta-galactosidase gene was isolated from pDUC/Z (Liang et al (1993) Virology 195:42-50) after cleavage with NcoI and HindIII and cloned into pSM71-del1-SV at the BamHI site to put the beta-galactosidase gene under the control of the SV40 regulatory sequences to obtain pSM71-Z.

Modes of Carrying Out the Invention

The practice of the present invention will employ, unless otherwise indicated, conventional microbiology, immunology, virology, molecular biology, and recombinant DNA techniques which are within the skill of the art. These techniques are fully explained in the literature. See, e.g., Maniatis et al., Molecular Cloning: A Laboratory Manual (1982); DNA Cloning: A Practical Approach, vols. I & II (D. Glover, ed.); Oligonucleotide Synthesis (N. Gait, ed. (1984)); Nucleic Acid Hybridization (B. Hames & S. Higgins, eds. (1985)); Transcription and Translation (B. Hames & S. Higgins, eds. (1984)); Animal Cell Culture (R. Freshney, ed. (1986)); Perbal, A Practical Guide to Molecular Cloning (1984). Sambrook et al., Molecular Cloning: A Laboratory Manual (2nd Edition); vols. I, II & III (1989).

A. Definitions

In describing the present invention, the following terminology, as defined below, will be used.

A "replicon" is any genetic element (e.g., plasmid, chromosome, virus) that functions as an autonomous unit of DNA replication in vivo; i.e., is capable of replication under its own control.

A "vector" is a replicon, such as a plasmid, phage, cosmid or virus, to which another DNA segment

may be attached so as to bring about the replication of the attached segment.

By "live virus" is meant, in contradistinction to "killed" virus, a virus which is capable of producing identical progeny in tissue culture and inoculated animals.

A "helper-free virus vector" is a vector that does not require a second virus or a cell line to supply something defective in the vector.

A "double-stranded DNA molecule" refers to the polymeric form of deoxyribonucleotides (adenine, guanine, thymine, or cytosine) in its normal, double-stranded helix. This term refers only to the primary and secondary structure of the molecule, and does not limit it to any particular tertiary forms. Thus, this term includes double-stranded DNA found, inter alia, in linear DNA molecules (e.g., restriction fragments of DNA from viruses, plasmids, and chromosomes). In discussing the structure of particular double-stranded DNA molecules, sequences may be described herein according to the normal convention of giving only the sequence in the 5′ to 3′ direction along the nontranscribed strand of DNA (i.e., the strand having the sequence homologous to the mRNA).

A DNA "coding sequence" is a DNA sequence which is transcribed and translated into a polypeptide in vivo when placed under the control of appropriate regulatory sequences. The boundaries of the coding sequence are determined by a start codon at the 5′ (amino) terminus and a translation stop codon at the 3′ (carboxy) terminus. A coding sequence can include, but is not limited to, procaryotic sequences, cDNA from eucaryotic mRNA, genomic DNA sequences from eucaryotic (e.g., mammalian) DNA, viral DNA, and even synthetic DNA sequences. A polyadenylation signal and transcription termination sequence will usually be located 3′ to the coding sequence.

A "transcriptional promoter sequence" is a DNA regulatory region capable of binding RNA

polymerase in a cell and initiating transcription of a downstream (3′ direction) coding sequence. For purposes of defining the present invention, the promoter sequence is bound at the 3′ terminus by the translation start codon (ATG) of a coding sequence and extends upstream (5′ direction) to include the minimum number of bases or elements necessary to initiate transcription at levels detectable above background. Within the promoter sequence will be found a transcription initiation site (conveniently defined by mapping with nuclease S1), as well as protein binding domains (consensus sequences) responsible for the binding of RNA polymerase. Eucaryotic promoters will often, but not always, contain "TATA" boxes and "CAAT" boxes. Procaryotic promoters contain Shine-Dalgarno sequences in addition to the -10 and -35 consensus sequences.

DNA "control sequences" refer collectively to promoter sequences, ribosome binding sites, polyadenylation signals, transcription termination sequences, upstream regulatory domains, enhancers, and the like, which collectively provide for the transcription and translation of a coding sequence in a host cell.

A coding sequence or sequence encoding is "operably linked to" or "under the control of" control sequences in a cell when RNA polymerase will bind the promoter sequence and transcribe the coding sequence into mRNA, which is then translated into the polypeptide encoded by the coding sequence.

A "host cell" is a cell which has been transformed, or is capable of transformation, by an exogenous DNA sequence.

A cell has been "transformed" by exogenous DNA when such exogenous DNA has been introduced inside the cell membrane. Exogenous DNA may or may not be integrated (covalently linked) to chromosomal DNA making up the genome of the cell. In procaryotes and yeasts, for example, the exogenous DNA may be

maintained on an episomal element, such as a plasmid. A stably transformed cell is one in which the exogenous DNA has become integrated into the chromosome so that it is inherited by daughter cells through chromosome replication. For mammalian cells, this stability is demonstrated by the ability of the cell to establish cell lines or clones comprised of a population of daughter cell containing the exogenous DNA.

A "clone" is a population of daughter cells derived from a single cell or common ancestor. A "cell line" is a clone of a primary cell that is capable of stable growth in vitro for many generations.

Two polypeptide sequences are "substantially homologous" when at least about 80% (preferably at least about 90%, and most preferably at least about 95%) of the amino acids match over a defined length of the molecule.

Two DNA sequences are "substantially homologous" when they are identical to or not differing in more that 40% of the nucleotides, more preferably about 20% of the nucleotides, and most preferably about 10% of the nucleotides.

DNA sequences that are substantially homologous can be identified in a Southern hybridization experiment under, for example, stringent conditions, as defined for that particular system. Defining appropriate hybridization conditions is within the skill of the art. See, e.g., Maniatis et al., supra; DNA Cloning, vols. I & II, supra; Nucleic Acid Hybridization, supra.

A "heterologous" region of a DNA construct is an identifiable segment of DNA within or attached to another DNA molecule that is not found in association with the other molecule in nature. Thus, when the heterologous region encodes a viral gene, the gene will usually be flanked by DNA that does not flank the viral gene in the genome of the source virus

or virus-infected cells. Another example of the heterologous coding sequence is a construct where the coding sequence itself is not found in nature (e.g., synthetic sequences having codons different from the native gene). Allelic variation or naturally occurring mutational events do not give rise to a heterologous region of DNA, as used herein.

"Bovine host" refers to cattle of any breed, adult or infant.

The term "protein" is used herein to designate a polypeptide or glycosylated polypeptide, respectively, unless otherwise noted. The term "polypeptide" is used in its broadest sense, i.e., any polymer of amino acids (dipeptide or greater) linked through peptide bonds. Thus, the term "polypeptide" includes proteins, oligopeptides, protein fragments, analogs, muteins, fusion proteins and the like.

"Fusion protein" is usually defined as the expression product of a gene comprising a first region encoding a leader sequence or a stabilizing polypeptide, and a second region encoding a heterologous protein. It involves a polypeptide comprising an antigenic protein fragment or a full length BAV protein sequence as well as (a) heterologous sequence(s), typically a leader sequence functional for secretion in a recombinant host for intracellularly expressed polypeptide, or an N-terminal sequence that protects the protein from host cell proteases, such as SOD. An antigenic protein fragment is usually about 5-7 amino acids in length.

"Native" proteins or polypeptides refer to proteins or polypeptides recovered from BAV or BAV-infected cells. Thus, the term "native BAV polypeptide" would include naturally occurring BAV proteins and fragments thereof. "Non-native" polypeptides refer to polypeptides that have been produced by recombinant DNA methods or by direct synthesis. "Recombinant" polypeptides refers to polypeptides produced by recombinant DNA techniques;

i.e., produced from cells transformed by an exogenous DNA construct encoding the desired polypeptide.

A "substantially pure" protein will be free of other proteins, preferably at least 10% homogeneous, more preferably 60% homogeneous, and most preferably 95% homogeneous.

An "antigen" refers to a molecule containing one or more epitopes that will stimulate a host's immune system to make a humoral and/or cellular antigen-specific response. The term is also used interchangeably with "immunogen."

A "hapten" is a molecule containing one or more epitopes that does not stimulate a host's immune system to make a humoral or cellular response unless linked to a carrier.

The term "epitope" refers to the site on an antigen or hapten to which a specific antibody molecule binds or is recognized by T cells. The term is also used interchangeably with "antigenic determinant" or "antigenic determinant site."

An "immunological response" to a composition or vaccine is the development in the host of a cellular and/ or antibody-mediated immune response to the composition or vaccine of interest. Usually, such a response consists of the subject producing antibodies, B cells, helper T cells, suppressor T cells, and/or cytotoxic T cells directed specifically to an antigen or antigens included in the composition or vaccine of interest.

The terms "immunogenic polypeptide" and "immunogenic amino acid sequence" refer to a polypeptide or amino acid sequence, respectively, which elicit antibodies that neutralize viral infectivity, and/or mediate antibody-complement or antibody dependent cell cytotoxicity to provide protection of an immunized host. An "immunogenic polypeptide" as used herein, includes the full length (or near full length) sequence of the desired protein or an immunogenic fragment thereof.

By "immunogenic fragment" is meant a fragment of a polypeptide which includes one or more epitopes and thus elicits antibodies that neutralize viral infectivity, and/or mediates antibody-complement or antibody dependent cell cytotoxicity to provide protection of an immunized host. Such fragments will usually be at least about 5 amino acids in length, and preferably at least about 10 to 15 amino acids in length. There is no critical upper limit to the length of the fragment, which could comprise nearly the full length of the protein sequence, or even a fusion protein comprising fragments of two or more of the antigens. The term "treatment" as used herein refers to treatment of a mammal, such as bovine or the like, either (i) the prevention of infection or reinfection (prophylaxis), or (ii) the reduction or elimination of symptoms of an infection. The vaccine comprises the recombinant BAV itself or recombinant antigen produced by recombinant BAV.

By "infectious" is meant having the capacity to deliver the viral genome into cells.

B. General Method

The present invention identifies and provides a means of deleting part or all of the nucleotide sequence of bovine adenovirus E1 and/or E3 gene regions to provide sites into which heterologous or homologous nucleotide sequences encoding foreign genes or fragments thereof can be inserted to generate bovine adenovirus recombinants. By "deleting part of" the nucleotide sequence is meant using conventional genetic engineering techniques for deleting the nucleotide sequence of part of the E1 and/or E3 region.

Various foreign genes or coding sequences (prokaryotic, and eukaryotic) can be inserted in the bovine adenovirus nucleotide sequence, e.g.,DNA, in accordance with the present invention, particularly to provide protection against a wide range of diseases

and many such genes are already known in the art. The problem heretofore having been to provide a safe, convenient and effective vaccine vector for the genes or coding sequences.

It is also possible that only fragments of nucleotide sequences of genes can be used (where these are sufficient to generate a protective immune response) rather than the complete sequence as found in the wild-type organism. Where available, synthetic genes or fragments thereof can also be used. However, the present invention can be used with a wide variety of genes, fragment and the like, and is not limited to those set out above.

In some cases the gene for a particular antigen can contain a large number of introns or can be from an RNA virus, in these cases a complementary DNA copy (cDNA) can be used.

In order for successful expression of the gene to occur, it can be inserted into an expression vector together with a suitable promoter including enhancer elements and polyadenylation sequences. A number of eucaryotic promoter and polyadenylation sequences which provide successful expression of foreign genes in mammalian cells and how to construct expression cassettes, are known in the art, for example in U.S. patent 5,151,267, the disclosures of which are incorporated herein by reference. The promoter is selected to give optimal expression of immunogenic protein which in turn satisfactorily leads to humoral, cell mediated and mucosal immune responses according to known criteria.

The foreign protein produced by expression *in vivo* in a recombinant virus-infected cell may be itself immunogenic. More than one foreign gene can be inserted into the viral genome to obtain successful production of more than one effective protein.

Thus with the recombinant virus of the present invention, it is possible to provide protection against a wide variety of diseases

affecting cattle. Any of the recombinant antigenic determinant or recombinant live virus of the invention can be formulated and used in substantially the same manner as described for the antigenic determinant vaccines or an live vaccine vectors.

The antigens used in the present invention can be either native or recombinant antigenic polypeptides or fragments. They can be partial sequences, full-length sequences, or even fusions (e.g., having appropriate leader sequences for the recombinant host, or with an additional antigen sequence for another pathogen). The preferred antigenic polypeptide to be expressed by the virus systems of the present invention contain full-length (or near full-length) sequences encoding antigens. Alternatively, shorter sequences that are antigenic (i.e., encode one or more epitopes) can be used. The shorter sequence can encode a "neutralizing epitope," which is defined as an epitope capable of eliciting antibodies that neutralize virus infectivity in an in vitro assay. Preferably the peptide should encode a "protective epitope" that is capable of raising in the host an "protective immune response;" i.e., an antibody- and/or a cell-mediated immune response that protects an immunized host from infection.

The antigens used in the present invention, particularly when comprised of short oligopeptides, can be conjugated to a vaccine carrier. Vaccine carriers are well known in the art: for example, bovine serum albumin (BSA), human serum albumin (HSA) and keyhole limpet hemocyanin (KLH). A preferred carrier protein, rotavirus VP6, is disclosed in EPO Pub. No. 0259149, the disclosure of which is incorporated by reference herein.

Genes for desired antigens or coding sequences thereof which can be inserted include those of organisms which cause disease in mammals, particularly bovine pathogens such as bovine rotavirus, bovine coronavirus, bovine herpes virus

type 1, bovine respiratory syncytial virus, bovine parainfluenza virus type 3 (BPI-3), bovine diarrhea virus, Pasteurella haemolytica, Haemophilus somnus and the like. The vaccines of the invention carrying foreign genes or fragments can also be orally administered in a suitable oral carrier, such as in an enteric-coated dosage form. Oral formulations include such normally-employed excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin cellulose, magnesium carbonate, and the like. Oral vaccine compositions may be taken in the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations, or powders, containing from about 10% to about 95% of the active ingredient, preferably about 25% to about 70%. An oral vaccine may be preferable to raise mucosal immunity in combination with systemic immunity, which plays an important role in protection against pathogens infecting the gastrointestinal tract.

In addition, the vaccine be formulated into a suppository. For suppositories, the vaccine composition will include traditional binders and carriers, such as polyalkaline glycols or triglycerides. Such suppositories may be formed from mixtures containing the active ingredient in the range of about 0.5% to about 10% (w/w), preferably about 1% to about 2%.

Protocols for administering to animals the vaccine composition(s) of the present invention are within the skill of the art in view of the present disclosure. Those skilled in the art will select a concentration of the vaccine composition in a dose effective to elicit an antibody and/or T-cell mediated immune response to the antigenic fragment. Within wide limits, the dosage is not believed to be critical. Typically, the vaccine composition is administered in a manner which will deliver between about 1 to about 1,000 micrograms of the subunit

antigen in a convenient volume of vehicle, e.g., about 1-10 cc. Preferably, the dosage in a single immunization will deliver from about 1 to about 500 micrograms of subunit antigen, more preferably about 5-10 to about 100-200 micrograms (e.g., 5-200 micrograms).

The timing of administration may also be important. For example, a primary inoculation preferably may be followed by subsequent booster inoculations if needed. It may also be preferred, although optional, to administer a second, booster immunization to the animal several weeks to several months after the initial immunization. To insure sustained high levels of protection against disease, it may be helpful to readminister a booster immunization to the animals at regular intervals, for example once every several years. Alternatively, an initial dose may be administered orally followed by later inoculations, or vice versa. Preferred vaccination protocols can be established through routine vaccination protocol experiments.

The dosage for all routes of administration of *in vivo* recombinant virus vaccine depends on various factors including, the size of patient, nature of infection against which protection is needed, carrier and the like and can readily be determined by those of skill in the art. By way of non-limiting example, a dosage of between 10^3 pfu and 10^8 pfu and the like can be used. As with *in vitro* subunit vaccines, additional dosages can be given as determined by the clinical factors involved.

In one embodiment of the invention, a number of recombinant cell lines are produced according to the present invention by constructing an expression cassette comprising the BAV E1 region and transforming host cells therewith to provide cell lines or cultures expressing the E1 proteins. These recombinant cell lines are capable of allowing a recombinant BAV, having an E1 gene region deletion replaced by

heterologous nucleotide sequence encoding for a foreign gene or fragment, to replicate and express the desired foreign gene or fragment thereof which is encoded within the recombinant BAV. These cell lines are also extremely useful in generating recombinant BAV, having an E3 gene deletion replaced by heterologous nucleotide sequence encoding for a foreign gene or fragment, by in vivo recombination following DNA-mediated cotransfection.

In one embodiment of the invention, the recombinant expression cassette can be obtained by cleaving the wild-type BAV genome with an appropriate restriction enzyme to produce a DNA fragment representing the left end or the right end of the genome comprising E1 or E3 gene region sequences, respectively and inserting the left or right end fragment into a cloning vehicle, such as plasmid and thereafter inserting at least one DNA sequence encoding a foreign protein, into E1 or E3 deletion with or without the control of an exogenous promoter. The recombinant expression cassette is contacted with the wild-type BAV DNA through homologous recombination or other conventional genetic engineering method within an E1 transformed cell line to obtain the desired recombinant.

The invention also includes an expression system comprising an bovine adenovirus expression vector wherein a heterologous nucleotide, e.g. DNA, replaces part or all of the E3 region and/or part or all of the E1 region. The expression system can be used wherein the foreign nucleotide sequences, e.g. DNA, is with or without the control of any other heterologous promoter.

The BAV E1 gene products of the adenovirus of the invention transactivate most of the cellular genes, and therefore, cell lines which constitutively express E1 proteins can express cellular polypeptides at a higher level than normal cell lines. The recombinant mammalian, particularly bovine, cell lines

of the invention can be used to prepare and isolate polypeptides,, including those such as (a) proteins associated with adenovirus E1A proteins: e.g. p300, retinoblastoma(Rb) protein, cyclins, kinases and the like.; (b) proteins associated with adenovirus E1B protein: e.g. p53 and the like.; (c) growth factors, such as epidermal growth factor (EGF), transforming growth factor (TGF) and the like; (d) receptors such as epidermal growth factor receptor (EGF-R), fibroblast growth factor receptor (FGF-R), tumor necrosis factor receptor (TNF-R), insulin-like growth factor receptor (IFG-R), major histocompatibility complex class I receptor and the like; (e) proteins encoded by proto-oncogenes such as protein kinases (tyrosine-specific protein kinases and protein kinases specific for serine or threonine), p21 proteins (guanine nucleotide-binding proteins with GTPase activity and the like; (f) other cellular proteins such as actins, collagens, fibronectins, integrins, phospholipids, proteoglycans, histones and the like, and (g) proteins involved in regulation of transcription such as TATA-box-binding protein (TBP), TBP-associated factors (TAFs). SP1 binding protein and the like.

The invention also includes a method for providing gene therapy to a mammal in need thereof to control a gene deficiency which comprises administering to said mammal a live recombinant bovine adenovirus containing a foreign nucleotide sequence encoding a non-defective form of said gene under conditions wherein the recombinant virus vector genome is incorporated into said mammalian genome or is maintained independently and extrachromosomally to provide expression of the required gene in the target organ or tissue. These kinds of techniques are recently being used by those of skill in the art to replace a defective gene or portion thereof. Examples of foreign genes nucleotide sequences or portions thereof that can be incorporated for use in a

conventional gene therapy include, cystic fibrosis transmembrane conductance regulator gene, human minidystrophin gene, alpha1-antitrypsin gene and the like.

Examples

Described below are examples of the present invention. These examples are provided only for illustrative purposes and are not intended to limit the scope of the present invention in any way. In light of the present disclosure, numerous embodiments within the scope of the claims will be apparent to those of ordinary skill in the art. The contents of the references cited in the specification are incorporated by reference herein.

Cells and viruses

Cell culture media and reagents were obtained from GIBCO/BRL Canada (Burlington, Ontario, Canada). Media were supplemented with 25 mM Hepes and 50 μg/ml gentamicin. MDBK cells or MDBK cells transformed with a plasmid containing BAV3 E1 sequences were grown in MEM supplemented with 10% Fetal bovine serum. The wild-type BAV3 ((strain WBR-1) (Darbyshire et al, 1965 J. Comparative Pathology 75:327) was kindly provided by Dr. B. Darbyshire, University of Guelph, Guelph, Canada) and BAV3-luciferase recombinants working stocks and virus titrations were done in MDBK cells.

Enzymes, bacteria and plasmids

Restriction endonucleases, polymerase chain reaction (PCR) and other enzymes required for DNA manipulations were purchased from Pharmacia LKB Biotechnology (Canada) Ltd. (Dorval, Quebec, Canada), Boehringer-Mannheim, Inc. (Laval or Montreal, Quebec, Canada), New England BioLabs (Beverly, MA), or GIBCO/BRL Canada (Burlington, Ontario, Canada) and used as per manufacturer's instructions. Restriction

enzyme fragments of BAV3 DNA were inserted into pUC18 or pUC19 (Yanich-Penon et al (1985) Gene 33:103-109) following standard procedures (Sambrook et al (1989) Molecular Cloning: A Laboratory Manual, 2nd ed. Cold Spring Harbour Laboratory, New York). *E. coli* strain DH5 (*sup*E44 *hsd*R17 *rec*A1 *end*A1 *gyr*A96 *thi*-1 *rel*A1) was transformed with recombinant plasmids by electroporation (Dower et al. (1988) Nuc. Acids Res., 16:6127-6145). Plasmid DNA was prepared using the alkaline lysis procedure (Bernboim and Doly (1978) Nuc. Acids Res., 7:1513-1523). The plasmid, pSVOA/L containing the entire cDNA encoding firefly luciferase (de Wet et al (1987) Mol. Cell. Biol. 7:725-737), was a gift from D.R. Helinski, University of California, San Diego, La Jolla, CA.

Construction of recombinant BAV3

MDBK cells transformed with a plasmid containing BAV3 E1 sequences were cotransfected with the wt BAV3 DNA digested with PvuI and the plasmid, pSM51-Luc (Figs. 9 and 10) using the lipofection-mediated cotransfection protocol (GIBCO/BRL, Life Technologies, Inc., Grand Island, NY). The virus plaques produced following cotransfection were isolated, plaque purified and the presence of the luciferase gene in the BAV3 genome was detected by agarose gel electrophoresis of recombinant virus DNA digested with appropriate restriction enzymes.

Southern blot and hybridization

Mock or virus-infected MDBK cells were harvested in lysis buffer (500 µg/ml pronase in 0.01 M Tris, pH 7.4, 0.01 M EDTA, 0.5% SDS) and DNA was extracted (Graham et al (1991) Manipulation of adenovirus vectors In: Methods and Molecular Biology, 7:Gene Transfer and Expression Techniques (Eds. Murray and Walker) Humana Press, Clifton, N.J. pp. 109-128). 100 ng DNA was digested either with BamHI, EcoRI or XbaI and resolved on a 1% agarose gel by

electrophoresis. DNA bands from the agarose gel were transferred to a *GeneScreenPlus*™ membrane (Du Pont Canada Inc. (NEN Products), Lachine, Quebec, Canada) by the capillary blot procedure (Southern, E.M. (1975) J. Mol. Biol. 98:503-517). Probes were labeled with ^{32}P using an Oligolabeling Kit (Pharmacia LKB Biotechnology (Canada) Ltd., Dorval, Quebec, Canada) and the unincorporated label was removed by passing the labeled probe through a sephadex G-50 column (Sambrook et al (1989) supra). Probes were kept in a boiling water bath for 2 min and used in hybridization experiments following *GeneScreenPlus*™ hybridization protocol. The DNA bands which hybridized with the probe were visualized by autoradiography.

Luciferase assays

The protocol was essentially the same as described (Mittal et al (1993) Virus Res. 28:67-90). Briefly, MDBK cell monolayers in 25 mm multi-well dishes (Corning Glass Works, Corning, NY) were infected in duplicate either with BAV3-Luc (3.1) or BAV3-Luc (3.2) at a m.o.i. of 50 p.f.u. per cell. At indicated time points post-infection, recombinant virus-infected cell monolayers were washed once with PBS (0.137 M NaCl, 2.7 mM KCl, 8 mM Na_2HPO_4, 1.5 mM KH_2PO_4) and harvested in 1 ml luciferase extraction buffer (100 mM potassium phosphate, pH 7.8, 1 mM dithiothreitol). The cell pellets were resuspended in 200 µl of luciferase extraction buffer and lysed by three cycles of freezing and thawing. The supernatants were assayed for luciferase activity. For the luciferase assay, 20 µl of undiluted or serially diluted cell extract was mixed with 350 µl of luciferase assay buffer (25 mM glycylglycine, pH 7.8, 15 mM $MgCl_2$, 5 mM ATP) in a 3.5 ml tube (Sarstedt Inc., St-Laurent, Quebec, Canada). Up to 48 tubes can be kept in the luminometer rack and the equipment was programed to inject 100 µl of luciferin solution (1 mM luciferin in 100 mM potassium phosphate buffer, pH

7.8) in the tube present in the luminometer chamber to start the enzyme reaction. The Luminometer (Packard Picolite Luminometer, Packard Instrument Canada, Ltd., Mississauga, Ontario, Canada) used in the present study produced 300 to 450 light units of background count in a 10 sec reaction time. Known amounts of the purified firefly luciferase were used in luciferase assays to calculate the amount of active luciferase present in each sample.

Western blotting

Mock or virus-infected MDBK cells were lysed in 1:2 diluted 2X loading buffer (80 mM Tris-HCl, pH 6.8, 0.67 M urea, 25% glycerol, 2.5% SDS, 1 M mercaptoethanol, 0.001% bromophenol blue), boiled for 3 min and then centrifuged to pellet cell debris. Proteins were separated by SDS-polyacrylamide gel electrophoresis (SDS-PAGE) on 0.1% SDS-10% polyacrylamide gels (Laemmli, et al (1970) Nature 227:680-685). After the end of the run, polypeptide bands in the gel were electrophoretically transferred to a nitrocellulose membrane (Bio-Rad Laboratories, Richmond, CA). The membrane was incubated at room temperature for 2 h with 1:4000 diluted rabbit anti-luciferase antibody (Mittal et al (1993) supra). The binding of anti-luciferase antibody to the specific protein band/s on the membrane was detected with 1:5000 diluted horseradish peroxidase conjugated-goat anti-rabbit IgG (Bio-Rad Laboratories, Richmond, CA) and with an ECL Western blotting detection system (Amersham Canada Ltd., Oakville, Ontario).

Example 1 Cloning of BAV3 E1 Region DNA for sequencing

To complement the restriction site (Kurokawa et al, 1978 J. Virol., 28:212-218; Hu et al, 1984 J. Virol. 49:604-608) other restriction enzyme sites in the BAV3 genome were defined. The 8.4 kilobase pair (kb) SalI B fragment which extends from the left end of the genome to approximately 24% was cloned into the

SmaI-SalI sites of pUC18 essentially as described previously (Graham et al, 1989 EMBO Journal 8:2077-2085). Beginning at the left end of the BAV3 genome, the relevant restriction sites used for subsequent subcloning and their approximate positions are: SacI (2%), EcoRI (3.5%), HindIII (5%), SacI (5.5%), SmaI (5.6%) and HindIII (11%). Through the use of appropriate restriction enzymes, the original plasmid was collapsed to contain smaller inserts which could be sequenced using the pUC universal primers. Some fragments were also subcloned in both pUC18 and pUC19 to allow confirmational sequencing in both directions. These procedures, together with the use of twelve different oligonucleotide primers hybridizing with BAV3 sequences, allowed to sequence the BAV3 genome from its left end to the HindIII site at 11%.

To ensure that some features of the sequence obtained were not unique to the initial clone selected for sequencing, two more pUC19 clones were prepared containing the SalI fragment from a completely independent DNA preparation. These clones were used to confirm the original sequence for the region from approximately 3% to 5.5% of the BAV3 genome.

DNA sequencing reactions were based on the chain-termination method (Sanger et al. 1977 PNAS, USA 74:5463-5467) and manual sequencing followed the DNA sequencing protocol described in the Sequenase™ kit produced by US Biochemical. [α-^{35}S]dATPs was obtained from Amersham Canada Ltd. All oligonucleotides used as primers were synthesized by the Central Facility of the Molecular Biology and Biotechnology Institute (MOBIX) at McMaster University, Hamilton, Ontario. The entire region (0 to 11%) of the BAV3 genome was sequenced by at least two independent determinations for each position by automated sequencing on a 373A DNA Sequencer (Applied Biosystems) using Taq-Dye terminators. Over half of the region was further sequenced by manual procedures to confirm overlaps and other regions of interest.

DNA sequence analysis and protein comparisons were carried out on a MICROGENIE program.

Example 2 Coding Sequences of the BAV3 E1 Region

BAV3 genomic DNA, from the left end of the genome to the HindIII site at approximately 11%, was cloned into plasmids and sequenced by a combination of manual and automated sequencing. An examination of the resultant BAV3 E1 genomic sequence (Fig 1) revealed a number of interesting features relevant both to transactivation and to other functions associated with adenovirus E1 proteins. On the basis of open reading frames (ORFs) it was possible to assign potential coding regions analogous to those defined in human Ad5 (HAd5). As shown in Fig 1, ORFs corresponding roughly to the first exon and unique region of HAd5 E1A as well are ORFs corresponding to the 19k and 58k proteins of E1B and the ORF corresponding to protein IX were all defined in this sequence. The open reading frame defining the probable E1A coding region begins at the ATG at nt 606 and continues to a probable splice donor site at position 1215. The first consensus splice acceptor site after this is located after nt 1322 and defines an intron of 107 base pairs with an internal consensus splice branching site at position 1292. The putative BAV3 E1A polypeptide encoded by a message corresponding to these splice sites would have 211 amino acids and a unmodified molecular weight of 23,323. The major homology of the protein encoded by this ORF and HAd5 E1A is in the residues corresponding to CR3 (shown in Fig 2). The homology of amino acid sequences on both sides of the putative intron strengthens the assignment of probable splice donor and acceptor sites. The CR3 has been shown to be of prime importance in the transactivation activity of HAd5 EIA gene products. As seen in Fig. 2A the homology of this sequence in the BAV3 protein to the corresponding region of the 289R E1A protein of HAd5

includes complete conservation of the $CysX_2CysX_{13}CysX_2Cys$ sequence motif which defines the metal binding site of this protein (Berg, 1986 Science 232:485-487) as well as conservation of a number of amino acids within this region and within the promoter binding region as defined by Lillie and Green 1989 Nature 338:39-44).

The only other region of significant homology between the BAV3 E1A protein and that of HAd5 was a stretch of amino acids known to be important in binding of the cellular Rb protein to the HAd5 E1A protein (Dyson et al, 1990 J. Virol. 64:1353-1356). As shown in Fig 2B, this sequence, which is located between amino acids 120 and 132 in the CR2 region of HAd5 E1A, is found near the amino (N-) terminus of the BAV3 protein between amino acids 26 and 37.

An open reading frame from the ATG at nt 1476 to the termination signal at 1947 defines a protein of 157 amino acids with two regions of major homology to the HAd5 E1B 19k protein. As shown in Fig 3 both the BAV3 and the HAd5 proteins have a centrally located hydrophobic amino acid sequence. The sequence in BAV3, with substitutions of valine for alanine and leucine for valine, should result in a somewhat more hydrophobic pocket than the corresponding HAd5 region. The other portion of HAd5 19k that may be conserved in the BAV3 protein is the serine rich sequence found near the N-terminus (residues 20 to 26) in HAd5 19k and near the C-terminus (residues 136 to 142) in the BAV3 protein (also shown in Fig 3).

On ORF beginning at the ATG at nt 1850 and terminating at nt 3110 overlaps the preceding BAV3 protein reading frame and thus has the same relationship to it as does the HAd5 E1B 56k protein to E1B 19k protein. As shown in Fig 4 this BAV3 protein of 420R and the corresponding HAd5 E1B 56k protein of 496R show considerable sequence homology over their C-terminal 346 residues. The N-terminal regions of

these proteins (not depicted in the figure) show no significant homology and differ in overall length.

Following the E1B ORFs, the open reading frame beginning at nt 3200 and ending at the translation terminator TAA at nt 3575 defines a protein of 125R with an unmodified molecular weight of 13,706. As seen in Fig 5 this protein shares some homology with the structural protein IX of HAd5 particularly in N-terminal sequences.

Possible Transcription Control Regions in BAV3 E1

The inverted terminal repeats (ITR) at the ends of the BAV3 genome have been shown to extend to 195 nt (Shinagawa et al, 1987 Gene 55:85-93). The GC-rich 3' portion of the ITR contains a number of consensus binding sites for the transcription stimulating protein SP1 (Dynan and Tijan (1983) Cell 35:79-87) and possible consensus sites for the adenovirus transcription factor (ATF) (Lee et al. (1987) Nature 325:368-372) occur at nts 60 and 220. While there are no exact consensus sites for the factors EF-1A (Bruder and Healing (1989) Mol. Cell Biol. 9:5143-5153) or E2F (Kovesdi et al, 1987 PNAS, USA 84:2180-2184) upstream of the ATG at nt 606, there are numerous degenerate sequences which may define the enhancer region comparable to that seen in HAd5 (Hearing and Shenk, 1986 Cell 45:229-236).

The proposed BAV3 E1A coding sequence terminates at a TGA residue at nt 1346 which is located within a 35 base pair sequence which is immediately directly repeated (see Fig 1). Two repeats of this sequence were detected in three independently derived clones for a plaque purified stock of BAV3. The number of direct repeats can vary in any BAV3 population though plaque purification allows for isolation of a relatively homogeneous population of viruses. That direct repeats in the sequences can function as promoter or enhancer elements for E1B transcription is being tested. There

are no strong polyA addition consensus sites between the E1A and the E1B coding sequences and in fact no AATAA sequence is found until after the protein IX coding sequences following E1B. The TATAAA sequence beginning at nt 1453 could function as the proximal promoter for E1B but it is located closer to the ATG at 1476 than is considered usual (McKnight et al, 1982 Science 217:316-322). The TATA sequence located further upstream immediately before the proposed E1A intron sequence also seems inappropriately positioned to serve as a transcription box for the E1B proteins. There are clearly some unique features in this region of the BAV3 genome.

The transcriptional control elements for the protein IX transcription unit are conventional and well defined. Almost immediately following the open reading frame for the larger E1B protein there is, at nt 3117, a SP1 binding sequence. This is followed at 3135 by a TATAAAT sequence which could promote a transcript for the protein IX open reading frame beginning at the ATG at 3200 and ending with the TAA at 3575. One polyA addition sequence begins within the translation termination codon and four other AATAA sequences are located at nts 3612, 3664, 3796 and 3932.

In keeping with the general organization of the E1A region of other adenoviruses, the BAV3 E1A region contains an intron sequence with translation termination codons in all three reading frames and which is therefore probably deleted by splicing from all E1A mRNA transcripts. The largest possible protein produced from the BAV3 E1A region will have 211 amino acid residues and is the equivalent of the 289 amino acid protein translated from the 13s mRNA of HAd5. Two striking features in a comparison of these proteins are the high degree of homology in a region corresponding to CR3 and the absence in BAV3 of most of amino acids corresponding to the second exon of HAd5. In fact the only amino acids encoded in the

second exon of BAV3 are, those which are considered to constitute part of CR3. A great deal of work carried out with HAd5 has identified the importance of the CR3 sequences in transactivation of other HAd5 genes. While a detailed analysis of the corresponding BAV3 region and its possible role in transactivation of BAV3 genes needs to be carried out, it is none-the-less interesting to note a couple of possibly pertinent features. The HAd5 CR3 region has been operationally subdivided into three regions (Lillie et al, 1989 Nature 338:39-44; see Fig 8); an N-terminal region from 139 to 153 which has four acidic residues and is thought to be important in transcription activation, a central, metal-binding, region defined by the Cys-X_2-Cys-X_{13}-CysX_2-Cys sequence which is essential for both promoter binding and activation, and a C-terminal region (residues 175-189) which is essential for promoter binding. Since, in most instances, E1A protein is thought not to interact directly with DNA (Ferguson et al 1985), the promoter binding regions may be involved in forming associations with proteins which then allow association with DNA. In Fig 2a the BAV3 E1A protein contains the central, metal binding domain and has considerable homology in the carboxy portion of this region. The BAV3 E1A protein also shows identity of sequence with HAd5 in the carboxy 6 amino acids of the promoter binding domain. These features may allow the BAV3 E1A protein to interact with the same transcription activating factors required for HAd5 E1A function. In contrast, except for a Glu-Glu pair there is little homology between the bovine and human viruses in the activation domain. The fact that this domain can be functionally substituted by a heterologous acidic activation sequence (Lillie et al, 1989 supra) suggests that protein specificity is not required in this region and this may allow the BAV3 E1A protein to function in the activation of BAV3 genes. The BAV3 E1A activation region contains six

acidic residues in the 18 residues amino to the metal binding domain.

The other interesting feature of BAV3 E1A, which is undoubtedly relevant to the oncogenic potential of this virus, is the presence of the sequence Asp27-Leu-Glu-Cys-His-Glu which conforms to, a core sequence known to be important in the binding of cellular Rb and related proteins by the transforming proteins of a number of DNA tumour viruses (Dyson et al, 1990 supra). From deletion mutant analysis there is a clear association between the potential of HAd5 E1A proteins to bind Rb and the ability of the protein to induce morphological transformation in appropriate cells (see references in Dyson et al, 1990 supra). The BAV3 E1A protein is distinct from its HAd5 counterpart in the relative position of this Rb binding sequence which is in the CR2 of HAd5 E1A and near the N-terminus of the BAV3 E1A protein.

Through the use of alternative splice sites HAd5 E1A transcripts can give rise to at least 5 distinct mRNA species (Berk et al, 1978 Cell 14:695-711; Stephens et al, 1987 EMBO Journal 6:2027-2035). Whether BAV3, like HAd5, can generate a number of different mRNA species through the use of alternative splice sites in the E1A transcripts remains to be determined. For example a potential splice donor site which could delete the sequence equivalent to the unique sequence of HAd5 is present immediately after nt 1080 but it is not known if this site is actually used.

HAd5 E1B encodes two proteins (19k and 56k) either of which can cooperate with E1A, by pathways which are additive and therefore presumably independent (McLorie et al, 1991 J. Gen. Virol. 72:1467-1471), to produce morphological transformation of cells in culture (see for example: Branton et al, 1985 supra; Graham, 1984 supra). The significance of the conservation of the hydrophobic stretch of amino

acids in the central portion of the shorter E1B proteins of HAd5 and BAV3 is not clear as yet. A second short region of homology Gln-Ser-Ser-X-Ser-Thr-Ser at residue 136 near the C-terminus of the BAV3 protein is located near the N-terminus at residue 20 in the HAd5 19k protein. The major difference in both length and sequence of the larger (420R) E1B protein of BAV3 from the corresponding HAd5 protein (496R) is confined to the N-terminus of these proteins. The two proteins show considerable evolutionary homology in the 345 amino acids that extend to their C-termini. A similar degree of homology extends into the N-terminal halves of protein IX of BAV3 and HAd5. Taken together these analyses suggest that while BAV3 and the human adenoviruses have diverged by simple point mutational events in some regions, more dramatic genetic events such as deletion and recombination may have been operating in other regions particularly those defining the junction between E1A and E1B.

Example 3 Cloning and sequencing of the BAV3 E3 and fibre genes

The general organization of adenovirus genomes seems to be relatively well conserved so it was possible to predict, from the locations of a number of HAd E3 regions, that BAV E3 should lie between map units (m.u.) 77 to 86. To prepare DNA for cloning and sequencing, BAV3 (strain WBR-1) was grown in Madin-Darby bovine kidney (MDBK) cells, virions were purified and DNA was extracted (Graham, F.L. & Prevec, L. (1991) Methods in Molecular Biology, vol. 7, Gene Transfer and Expression Protocols, pp. 109-146. Edited by E.J. Murray, Clifton, New Jersey; Humana Press.). Previously published restriction maps for *Eco*RI and *Bam*HI (Kurokawa et al., 1978) were confirmed (Fig. 6). The *Bam*HI D and *Eco*RI F fragments of BAV3 DNA were isolated and inserted into pUC18 and pUC19 vectors, and nested sets of deletions were made using exonuclease III and S1 nuclease (Henikoff, S.

(1984) Gene, 28:351-359). The resulting clones were sequenced by the dideoxynucleotide chain termination technique (Sanger, F., Nicklen, S. & Coulson, A.R. (1977) Proceedings of the National Academy of Sciences, U.S.A., 74:5463-5467). The nucleotide sequence from positions 1 to 287 was obtained from the right end of the *Bam*HI B fragment (Fig. 6). The sequence of the regions spanning (i) the *Bam*HI site at nucleotide 3306 and the *Eco*RI site at nucleotide 3406, and (ii) the *Eco*RI site at nucleotide 4801 and the nucleotide 5100 was obtained from a plasmid containing the *Xba*I C fragment (m.u. 83 to 100; not shown) using primers hybriding to BAV3 sequences. Analysis of the sequence was performed with the aid of the PC/GENE sequence analysis package developed by Amos Bairoch, Department of Medical Biochemistry, University of Geneva, Switzerland.

The 5100 nucleotide sequence which extends between 77 and 92 m.u. of the BAV3 genome is shown in Fig. 7. The upper strand contains 14 open reading frames (ORFs) which could encode polypeptides of 60 amino acid residues or more (Fig. 6 and 7). The lower strand contains no ORF encoding a protein of longer than 50 amino acids after an initiation codon. The predicted amino acid sequence for each ORF on the upper strand was analyzed for homology with predicted amino acid sequences from several sequenced Ads: HAd2 (Hérissé, J., Courtois, G. & Galibert, F. (1980) Nucleic Acids Research, 8:2173-2192; Hérissé, J., Courtois, G. & Galibert, F. (1981) Nucleic Acids Research, 9:1229-1249), -3(Signas, C., Akusjarvi, G. & Pettersson, U. (1985) Journal of Virology, 53:672-678.), -5(Cladaras, C. & Wold, W.S.M. (1985) Virology, 140:28-43), -7 (Hong, J.S., Mullis, K.G. & Engler, J.A. (1988) Virology, 167:545-553) and -35(Flomenberg, P.R., Chen, M. & Horwitz, M.S. (1988) Journal of Virology, 62:4431-4437), and murine Ad1 (MAd1) (Raviprakash, K.S., Grunhaus, A., El Kholy, M.A. & Horwitz, M.S. (1989) Journal of Virology, 63:5455-

5458) and canine Ad1 (CAd1) (Dragulev, B.P., Sira, S., Abouhaidar, M.G. & Campbell, J.B. (1991) Virology, 183:298-305). Three of the BAV3 ORFs exhibited homology with characterized HAd proteins pVIII, fibre and the 14.7K E3 protein. The amino acid sequence predicted from BAV3 ORF 1 shows overall identity of approximately 55% when compared to the C-terminal 75% of HAd2 pVIII (Cladaras & Wold, 1985, supra) (Fig. 8a), indicating that ORF 1 encodes the right end of BAd3 pVIII. Near the C-terminal end of BAd3 pVIII there is a 67 amino acid stretch (residues 59 to 125; Fig. 8a) which has 75% identity with HAd2 pVIII. This region has previously been shown to be highly conserved among different Ads (Cladaras & Wold, 1985, supra; Signas, C., Akusjarvi, G. & Pettersson, U. (1986) Gene, 50:173-184,; Raviprakash et al., 1989, supra; Dragulev et al., 1991, supra).

The fibre protein is present on the surface of the virion as long projections from each vertex of the icosahedral capsid and is involved in a number of Ad functions including attachment of the virus to the cell surface during infection, assembly of virions and antigenicity (Philipson, L. (1983) Current Topics in Microbiology and Immunology, 109:1-52). On the basis of the primary structure of HAd2 fibre protein, it has been proposed that the shaft region (between amino acid residues 40 and 400) is composed of a number of repeating structural motifs containing about 15 hydrophobic residues organized in two short β-sheets and two β-bends (Green, N.M., Wrigley, N.G., Russell, W.C., Martin, S.R. & McLachlan, A.D. (1983) EMBO Journal, 2:1357-1365). The amino acid sequences at the N terminus of the BAV3 ORF 6-encoded protein share about 60% identity with the HAd2 fibre protein tail, but there is little or no similarity in the knob region, and about 45% identity overall (Fig. 8c). The BAd3 fibre gene would encode a protein of 976 residues if no splicing occurs, i.e. 394 amino acid residues longer than the HAd2 fibre protein. The number of

repeating motifs in the shaft region of the fibre protein from different Ads varies between 28 and 23 (Signas et al., 1985, supra; Chroboczek, J. & Jacrot, B. (1987) Virology, 161:549-554; Hong et al., 1988, supra; Raviprakash et al., 1989, supra; Dragulev et al., 1991, supra). The BAV3 fibre protein can be organized into 52 such repeats in this region (not shown), which would account for most of the difference in size compared to those of HAd2, HAd3, HAD5, HAd7, CAd1 and MAd1 (Signas et al., 1985,supra; Hérissé et al., 1980,supra; Hérissé & Galibert, 1981, supra; Hong et al., 1988,supra; Raviprakash et al., 1989, supra; Dragulev et al., 1991, supra).

HAd2 and HAd5 E3 lies between the pVIII and the fibre genes an encodes at least 10 polypeptides (Cladaras & Wold, 1985,supra). The promoter for E3 of these two serotypes lies within the sequences encoding pVIII, about 320 bp 5′ of the termination codon. No consensus TATA box is found in the corresponding region of the BAV3 sequences. A non-canonical polyadenylation signal (ATAAA) for E3 transcripts is located at position 1723, between the end of the putative E3 region and the beginning of ORF 6, encoding the fibre protein, and two consensus signals are located within ORF 6 at positions 2575 and 3565. The polyadenylation signal for the fibre protein is located at nucleotide 4877. Six ORFs were identified in the BAV3 genome between the pVIII and the fibre genes, but only four (ORFs 2, 3, 4 and 5) have the potential to encode polypeptides of at least 50 amino acids after an initiation codon (Fig. 7). The amino acid sequence predicted to be encoded by ORF 2 is 307 residues long and contains eight potential N-glycosylation sites (Fig. 7) as well as a hydrophobic sequence which may be a potential transmembrane domain (PLLFAFVLCTGCAVLLTAFGPSILSGT) between residues 262 and 289. This domain may be a part of the protein homologous to the HAd2 and HAd5 19K E3 glycoprotein (Cladaras & Wold, 1985, supra), and the proposed CAd1

22.2K protein (Dragulev et al., 1991, supra), but ORF 2 does not show appreciable homology with these proteins. The ORF 4 shows approximately 44% identity with the 14.7K E3 protein of HAd5 (Fig. 6 and 8b), which has been shown to prevent lysis of virus-infected mouse cells by tumour necrosis factor (Gooding, L.R., Elmore, L.W., Tollefson, A.E., Brody, H.A. & Wold, W.S.M. (1988) Cell, 53:341-346; Wold, W.S.M. & Gooding, L.R. (1989) Molecular Biology and Medicine, 6:433-452). Analysis of the 14.7K protein sequence from HAd2, -3, -5 and -7 has revealed a highly conserved domain, which in HAd5 lies between amino acid residues 41 and 56 (Horton, T.M., Tollefson, A.E., Wold, W.S.M. & Gooding, L.R. (1990) Journal of Virology, 64:1250-1255). The corresponding region in the BAV3 ORF 4-encoded protein, between amino acids 70 and 85, contains 11 amino acids identical to those of the HAd5 14.7K protein conserved domain (Fig. 8b).

The BAV3 E3 region appears to be approximately 1.5kbp long, about half the size of those of HAd2 and -5 (Cladaras & Wold, 1985, supra), and novel splicing events in BAV3 E3 would be required to generate more homologues to the HAd3 E3 proteins. A similarly short E3 region has been reported for MAd1 (RAviprakash et al., 1989, supra) and CAd1 (Dragulev et al., 1991,supra).

Example 4 Construction of BAV3-luciferase recombinants

Adenovirus-based mammalian cell expression vectors have gained tremendous importance in the last few years as a vehicle for recombinant vaccine delivery, and also in gene therapy. BAV3-based expression vectors have a greater potential for developing novel recombinant vaccines for veterinary use. To show that BAV3 E3 gene products are not essential for virus growth in cultured cells and this locus could be used to insert foreign DNA sequences, a

1.7 kb fragment containing the firefly luciferase gene was introduced in the 696 bp deletion of the E3 region of the BAV3 genome in the E3 parallel orientation to generate a BAV3 recombinant.

The rationale of using the luciferase gene is that it acted as a highly sensitive reporter gene when introduced in the E3 region of the HAd5 genome to generate HAd5-Luc recombinants (Mittal et al (1993) Virus Res. 28:67-90).

To facilitate the insertion of the firefly luciferase gene into the E3 region of the BAV3 genome, a BAV3 E3 transfer vector containing the luciferase gene was constructed (Fig. 9). The BAV3 E3 region falls approximately between m.u. 77 and 82. In our first series of vectors we replaced a 696 bp XhoI-NcoI E3 deletion (between m.u. 78.8 and 80.8) with a NruI-SalI cloning sites for insertion of foreign genes to obtain pSM14del2. A 1716 bp BsmI-SspI fragment containing the luciferase gene was isolated and first inserted into an intermediate plasmid, pSM41, in the E3 locus at the SalI site by blunt end ligation to generate pSM41-Luc. The luciferase gene without any exogenous regulatory sequences, was inserted into the E3 locus in the same orientation as the E3 transcription unit. The kan^r gene was inserted into pSM41-Luc at the XbaI site present within the luciferase gene to generate an amp^r/kan^r plasmid, pSM41-Luc-Kan. A 7.7 kb fragment containing the BAV3 sequences along with the luciferase gene and the kan^r gene was obtained from pSM41-Luc-Kan by digestion with BamHI and inserted into an amp^r plasmid, pSM51 partially digested with BamHI to replace a 3.0 kb BamHI fragment (lies between m.u. 77.8 and 86.4) to generate a doubly resistant (kan^r & amp^r) plasmid, pSM51-Luc-Kan. The kan^r gene was deleted from pSM51-Luc-Kan by partial cleavage with XbaI to generate pSM51-Luc containing the luciferase gene in the E3-parallel orientation.

MDBK cells transformed with a plasmid containing the BAV3 E1 sequences was cotransfected with the wt BAV3 DNA digested with PvuI, which make two cuts within the BAV3 genome at m.u 65.7 and 71.1, and the plasmid, pSM51-Luc to rescue the luciferase gene in E3 of the BAV3 genome by *in vivo* recombination (Fig. 10). The digestion of the wt BAV3 DNA with PvuI was helpful in minimizing the generation of the wt virus plaques following cotransfection. The left end of the wt BAV3 genome represented by PvuI 'A' fragment falls between m.u. 0 and 65.7, and pSM51-Luc which extends between m.u. 31.5 and 100 (except for E3 deletion replaced with the luciferase gene) have sufficient overlapping BAV3 DNA sequences to generate recombinant viruses.

Two virus plaques were obtained in two independent cotransfection experiments which were grown in MDBK cells. The viral DNA from both plaques was extracted and analyzed by agarose gel electrophoresis after digesting either with BamHI, EcoRI or XbaI to identify the presence and orientation of the luciferase gene in the viral genome (data not shown). In the genomes of both recombinants, the luciferase gene was present in the E3 region in the E3 parallel orientation. The BAV3-luciferase recombinants were plaque purified and named BAV3-Luc (3.1) and BAV3-Luc (3.2) to represent plaques obtained from two independent experiments. Since both recombinant virus isolates were identical they will be referred to as BAV3-Luc. The presence of the luciferase gene in BAV3-Luc isolates are further confirmed by Southern blot analyses and luciferase assays using extracts from recombinant virus-infected cells.

Characterization of BAV3-recombinants

Southern blot analyses of the wt BAV3 and recombinants genomic DNA digested either with BamHI, EcoRI or XbaI, were carried out to confirm the

presence and orientation of the luciferase gene in the E3 locus and the deletion of the 696 bp XhoI-NcoI fragment from E3 of the BAV3-Luc genome (Fig. 11). When the blot was probed with a 696 XhoI-NcoI fragment of E3 of the BAV3 genome (panel A, lanes 4 to 9) no hybridization signal was detected with the DNA fragments from the recombinant viruses, however, the expected bands (3.0 kb BamHI, 8.1 kb EcoRI, and 18.5 kb XbaI) of the wt BAV3 DNA fragments (panel A, lanes 10 to 12) showed hybridization, confirming that the 696 bp XhoI-NcoI fragment of the E3 region was indeed deleted in the BAV3-Luc genomic DNA. In panel B, when an identical blot was probed with the luciferase gene, there were strong hybridization signals with the DNA fragments from the recombinant viruses (4.0 kb BamHI (lane 4 & 7), 6.0 kb & 3.2 kb EcoRI (lanes 5 & 8), 16.7 kb & 2.9 kb XbaI (lanes 6 & 9)). These results confirmed that the BAV3-Luc contains the luciferase gene in the E3 parallel orientation with a 696 bp XhoI-NcoI E3 deletion.

The growth characteristics of the recombinant viruses was compared with the wt BAV3 in a single step growth curve (Fig. 12). Virus titers in MDBK cells-infected with the wt BAV3 started increasing at 12 h post-infection reaching a maximum at 36-48 h post-infection and then declined thereafter. Virus titers of the recombinant viruses also started increasing at 12 h postinfection reaching a maximum at 48 h post-infection and then declined, however, the titers of recombinant viruses remained approximately one log lower than the wt virus. The plaque size of the recombinant viruses were also comparatively smaller than the wt virus (data not shown).

Kinetics of luciferase expression by BAV3-Luc

Luciferase activity in BAV3-Luc-infected MDBK cells was monitored at different times post-infection by luciferase assays (Fig. 13). A low level

of luciferase activity was first observed at 12 h post-infection reaching a peak at 30 h post-infection and then dropped subsequently. At 30 h post-infection, approximately 425 pg luciferase was detected in $4x10^5$ BAV3-Luc (3.1)-infected MDBK cells. In MDBK cells-infected with the wt BAV3, luciferase expression was not detected (data not shown). The kinetics of luciferase expression by BAV3-Luc (3.1) and BAV3-Luc (3.2) appears very much similar. The kinetics of luciferase expression also showed that the majority of enzyme expression in virus-infected cells seemed to occur late in infection. To determine luciferase expression in the absence of viral DNA replication, BAV3-Luc-infected MDBK cells were incubated in the presence of an inhibitor of DNA synthesis, 1-β-D-arabinofuranosyl cytosine (AraC) and luciferase activity was measured in virus-infected cell extracts at various times post-infection and compared to luciferase expression obtained in the absence of AraC (Fig. 14). When the recombinant virus-infected cells were incubated in the presence of AraC, luciferase expression at 18, 24 and 30 h post-infection was approximately 20-30% of the value obtained in the absence of AraC. These results indicated that the majority of luciferase expression in MDBK cells infected with BAV3-Luc took place after the onset of viral DNA synthesis. To confirm this MDBK cells-infected with the BAV3-Luc were grown in the absence or presence of AraC, harvested at 18 h, 24 h, and 30 h post-infection, viral DNA extracted and analyzed by dot bot analysis using pSM51-Luc (see Fig. 9) as a probe (data not shown). In the presence of AraC, viral DNA synthesis was severely reduced compared to viral DNA synthesis in the absence of AraC.

Western blot analysis of BAV3-Luc-infected cells

Luciferase was expressed as an active enzyme as determined by luciferase assays using extracts from

MDBK cells-infected with BAV3-Luc (see Fig. 13). The luciferase gene without any exogenous regulatory sequences was inserted into E3 of the BAV3 genome, therefore, there was a possibility of luciferase expression as a fusion protein with part of an E3 protein if the luciferase gene was in the same frame, Such as, F1 and F3 which represent open reading frames (ORFs) for E3 proteins (Fig. 15) or the fusion protein may arise due to recognition of an upstream initiation codon in the luciferase ORF. To explore this possibility we sequenced the DNA at the junction of the luciferase gene and the BAV3 sequences with the help of a plasmid, pSM51-Luc and a synthetic primer design to bind luciferase coding sequences near the initiation codon (data not shown). The luciferase coding region fell in frame F2. The luciferase initiation codon was the first start codon in this frame, however, the ORF started at 84 nucleotides upstream of the luciferase start codon. To further confirm that luciferase protein is of the same molecular weight as purified firefly luciferase, unlabeled mock-infected, wt BAV3-infected or BAV3-Luc-infected MDBK cell extracts were reacted with an anti-luciferase antibody in a Western blot (Fig. 16). A 62 kDa polypeptide band was visible in the BAV3-Luc (lane 3 and 4)-infected cell extracts which were of the same molecular weight as pure firefly luciferase (lane 5). We are not sure whether a band of approximately 30 kDa which also reacted with the anti-luciferase antibody in lanes 3 and 4 represented a degraded luciferase protein.

The majority of luciferase expression is probably driven from the major late promoter (MLP) to provide expression paralleling viral late gene expression, moreover, the enzyme expression seen in the presence of AraC may be taking place from the E3 promoter. In HAd5 vectors, foreign genes without any exogenous regulatory sequences when inserted in E3 also displayed late kinetics and were inhibited by

AraC. The BAV3 recombinant virus replicated relatively well in cultured cells but not as good as the wt BAV3. This is not surprising as infectious virus titers of a number of HAd5 recombinants were slightly lower than the wt HAd5 (Bett et al (1993) J. Virol. 67:5911-5921). This may be because of reduced expression of fiber protein in recombinant adenoviruses having inserts in the E3 region compared to the wt virus (Bett et al, supra and Mittal et al (1993) Virus Res. 28:67-90).

The E3 of BAV3 is approximately half the size of the E3 region of HAd2 or HAd5 and thus has the coding potential for only half the number of proteins compared to E3 of HAd2 or HAd5 (Cladaras et al (1985) Virology 140:28-43: Herisse et al (1980) Nuc. Acids Res. 8:2173-2192; Herisse et al (1981) Nuc. Acids Res. 9:1229-1249 and Mittal et al (1993 J. Gen. Virol. 73:3295-3000). BAV3 E3 gene products have been shown to be not required for virus growth in tissue culture. However, presently it is known that BAV3 E3 gene products also evade immune surveillance *in vivo* like HAds E3 proteins. One of the BAV3 E3 open reading frames (ORFs) has been shown to have amino acid homology with the 14.7 kDa E3 protein of HAds (Mittal et al (1993) supra). The 14.7 kDa E3 protein of HAds prevents lysis of virus-infected mouse cells by tumour necrosis factor (Gooding et al (1988) Cell 53:341-346 and Horton et al (1990) J. Virol. 64:1250-1255). The study of pathogenesis and immune responses of a series of BAV3 E3 deletion mutants in cattle provides very useful information regarding the role of E3 gene products in modulating immune responses in their natural host.

The BAV3-based vector has a 0.7 kb E3 deletion which can hold an insert up to 2.5 kb in size. The BAV3 E3 deletion can extend probably up to 1.4 kb which in turn would also increase the insertion capacity of this system. The role of the MLP and the E3 promoter is examined to determine their ability to

drive expression of a foreign gene inserted into E3 when a proper polyadenylation signal is provided. Exogenous promoters, such as, the simian virus 40 (SV40) promoter (Subramant et al (1983) Anal. Biochem. 135:1-15), the human cytomegalovirus immediate early promoter (Boshart et al (1985) Cell 43:215-222), and the human beta-actin promoter (Gunning et al (1987) PNAS, USA 84:4831-4835) are tested to evaluate their ability to facilitate expression of foreign genes when introduced into E3 of the BAV3 genome.

Recently HAd-based expression vectors are under close scrutiny for their potential use in human gene therapy (Ragot et al (1993) Nature 361:647-650; Rosenfeld et al (1991) Science 252:431-434; Rosenfeld et al (1992) Cell 68:141-155 and Stratford-Perricaudet et al (1990) Hum. Gene. Ther. 1:241-256). A preferable adenovirus vector for gene therapy would be one which maintains expression of the required gene for indefinite or for a long period in the target organ or tissue. It may be obtained if the recombinant virus vector genome is incorporate into the host genome or maintained its independent existence extrachromosomally without active virus replication. HAds replicate very well in human, being their natural host. HAds can be made defective in replication by deleting the E1 region, however, how such vectors would maintain the expression of the target gene in a required fashion is not very clear. Moreover, the presence of anti-HAds antibodies in almost every human being may create some problems with the HAd-based delivery system. The adenovirus genomes have a tendency to form circles in non-permissive cells. BAV-based vectors could provide a possible alternative to HAd-based vectors for human gene therapy. As BAV3 does not replicate in human, the recombinant BAV3 genomes may be maintained as independent circles in human cells providing expression of the essential protein for a long period of time.

The foreign gene insertion in animal adenoviruses is much more difficult than HAds because it is hard to develop a cell line which is also good for adenovirus DNA-mediated transfection. This may be one of the major reasons that the development of an animal adenovirus-based expression system has not been reported so far. It took us more than a year to isolate a cell line suitable for BAV3 DNA-mediated transfection. However, the rapid implementation of BAV-based expression vectors for the production of live virus recombinant vaccines for farm animals, is very promising. BAVs grow in the respiratory and gastrointestinal tracts of cattle, therefore, recombinant BAV-based vaccines have use to provide a protective mucosal immune response, in addition to humoral and cellular immune responses, against pathogens where mucosal immunity plays a major role in protection.

Example 5 Generation of cell lines transformed with the BAV3 E1 sequences

MDBK cells in monolayer cultures were transfected with pSM71-neo, pSM61-kan1 or pSM61-kan2 by a lipofection-mediated transfection technique (GIBCO/BRL, Life Technologies, Inc., Grand Island, NY). At 48 h after transfection, cells were maintained in the MEM supplemented with 5% fetal bovine serum and 700 μg/ml G418. The medium was changed every 3rd day. In the presence of G418, only those cells would grow which have stably incorporated the plasmid DNA used in transfection experiments into their genomes and are expressing the neo^r gene. The cells which have incorporated the neo^r gene might also have taken up the BAV3 E1 sequences and thus expressing BAV3 E1 protein/s. A number of neo^r (i.e., G418-resistant) colonies were isolated, expended and tested for the presence of BAV3 E1 message/s by Northern blot analyses using a DNA probe containing only the BAV3 E1 sequences. Expression of BAV3 E1

protein/s were confirmed by a complimentation assay using a HAd5 deletion mutant defective in E1 function due to an E1 deletion.

Fetal bovine kidney cells in monolayers were also transfected with pSM71-neo, pSM61kan-1 or pSM61-kan2 by the lipofection-mediated transfection technique, electroporation (Chu et al (1987) Nucl. Acids Res. 15:1311-1326), or calcium phosphate precipitation technique (Graham et al (1973) Virology 52:456-467). Similarly, a number of G418-resistant colonies were isolated, expended and tested for the presence of BAV3 E1 gene products as mentioned above.

Example 6 Generation of a BAV3 recombinant containing the beta-galactosidase gene as an E1 insert

As E1 gene products are essential for virus replication, adenovirus recombinants containing E1 inserts will grow only in a cell line which is transformed with the adenovirus E1 sequences and expresses E1. A number of cell line which are transformed with the BAV3 E1 sequences were isolated as described earlier. The technique of foreign gene insertions into the E1 regions is similar to the gene insertion into the E3 region of the BAV3 genome, however, for insertion into E1 there is a need of an E1 transfer plasmid which contains DNA sequences from the left end of the BAV3 genome, an appropriate deletion and a cloning site for the insertion of foreign DNA sequences. G418-resistant MDBK cell monolayers were cotransfected with the wild-type (wt) BAV3 DNA and pSM71-Z following the lipofection-mediated transfection procedure (GIBCO/BRL, Life Technologies, Inc., Grand Island, NY). The monolayers were incubated at 37°C under an agarose overlay. After a week post-incubation an another layer of overlay containing 300 ug/ml Blu-gal™ (GIBCO/BRL Canada, Burlington, Ontario, Canada) was put onto each monolayer. The blue plaques were isolated, plaque purified and the presence of the beta-galactosidase

gene in the BAV3 genome was identified by agarose gel electrophoresis of recombinant virus DNA digested with suitable restriction enzymes and confirmed by beta-galactosidase assays using extracts from recombinant virus infected cells.

Deposit of Biological Materials

The following materials were deposited and are maintained with the Veterinary Infectious Disease Organization (VIDO), Saskatoon, Saskatchewan, Canada.

The nucleotide sequences of the deposited materials are incorporated by reference herein, as well as the sequences of the polypeptides encoded thereby. In the event of any discrepancy between a sequence expressly disclosed herein and a deposited sequence, the deposited sequence is controlling.

Material	Internal Accession No.	Deposit Date
Recombinant plasmids		
pSM51	pSM51	Dec 6, 1993
pSM71	pSM71	Dec 6, 1993
Recombinant cell lines		
MDBK cells transformed with BAV3 E1 sequences(MDBK-BAVE1)		Dec 6, 1993
Fetal bovine kidney cells transformed with BAV3 E1 sequences(FBK-BAV-E1)		Dec 6, 1993

While the present invention has been illustrated above by certain specific embodiments, the specific examples are not intended to limit the scope of the invention as described in the appended claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:
(i) APPLICANT: UNIVERSITY OF SASKATCHEWAN
(ii) TITLE OF INVENTION: RECOMBINANT PROTEIN PRODUCTION IN BOVINE ADENOVIRUS EXPRESSION VECTOR SYSTEM
(iii) NUMBER OF SEQUENCES: 34
(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: SCOTT & AYLEN
(B) STREET: 60 QUEEN STREET
(C) CITY: OTTAWA
(D) PROVINCE: ONTARIO
(E) COUNTRY: CANADA
(F)POSTAL CODE: K1P 5Y7

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: JOAN M. VAN ZANT
(B) REFERENCE/DOCKET NUMBER: PAT 21976TW-90
(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: 1-416-368-2400
(B) TELEFAX: 1-416-363-7246

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4060 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: join(606..1215, 1323..1345)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

CATCATCAAT AATCTACAGT ACACTGATGG CAGCGGTCCA ACTGCCAATC ATTTTTGCCA 60

CGTCATTTAT GACGCAACGA CGGCGAGCGT GGCGTGCTGA CGTAACTGTG GGGCGGAGCG 120

CGTCGCGGAG GCGGCGGCGC TGGGCGGGGC TGAGGGCGGC GGGGGCGGCG CGCGGGGCGG 180

CGCGCGGGGC GGGGCGAGGG GCGGAGTTCC GCACCCGCTA CGTCATTTTC AGACATTTTT 240

TAGCAAATTT GCGCCTTTTG CAAGCATTTT TCTCACATTT CAGGTATTTA GAGGGCGGAT 300

TTTTGGTGTT CGTACTTCCG TGTCACATAG TTCACTGTCA ATCTTCATTA CGGCTTAGAC 360

AAATTTTCGG CGTCTTTTCC GGGTTTATGT CCCCGGTCAC CTTTATGACT GTGTGAAACA 420

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CACCTGCCCA TTGTTTACCC TTGGTCAGTT TTTTCGTCTC CTAGGGTGGG AACATCAAGA    480

ACAAATTTGC CGAGTAATTG TGCACCTTTT TCCGCGTTAG GACTGCGTTT CACACGTAGA    540

CAGACTTTTT CTCATTTTCT CACACTCCGT CGTCCGCTTC AGAGCTCTGC GTCTTCGCTG    600

CCACC ATG AAG TAC CTG GTC CTC GTT CTC AAC GAC GGC ATG AGT CGA         647
      Met Lys Tyr Leu Val Leu Val Leu Asn Asp Gly Met Ser Arg
        1               5                  10

ATT GAA AAA GCT CTC CTG TGC AGC GAT GGT GAG GTG GAT TTA GAG TGT       695
Ile Glu Lys Ala Leu Leu Cys Ser Asp Gly Glu Val Asp Leu Glu Cys
 15                 20                  25                  30

CAT GAG GTA CTT CCC CCT TCT CCC GCG CCT GTC CCC GCT TCT GTG TCA       743
His Glu Val Leu Pro Pro Ser Pro Ala Pro Val Pro Ala Ser Val Ser
                35                  40                  45

CCC GTG AGG AGT CCT CCT CCT CTG TCT CCG GTG TTT CCT CCG TCT CCG       791
Pro Val Arg Ser Pro Pro Pro Leu Ser Pro Val Phe Pro Pro Ser Pro
            50                  55                  60

CCA GCC CCG CTT GTG AAT CCA GAG GCG AGT TCG CTG CTG CAG CAG TAT       839
Pro Ala Pro Leu Val Asn Pro Glu Ala Ser Ser Leu Leu Gln Gln Tyr
        65                  70                  75

CGG AGA GAG CTG TTA GAG AGG AGC CTG CTC CGA ACG GCC GAA GGT CAG       887
Arg Arg Glu Leu Leu Glu Arg Ser Leu Leu Arg Thr Ala Glu Gly Gln
    80                  85                  90

CAG CGT GCA GTG TGT CCA TGT GAG CGG TTG CCC GTG GAA GAG GAT GAG       935
Gln Arg Ala Val Cys Pro Cys Glu Arg Leu Pro Val Glu Glu Asp Glu
 95                 100                 105                 110

TGT CTG AAT GCC GTA AAT TTG CTG TTT CCT GAT CCC TGG CTA AAT GCA       983
Cys Leu Asn Ala Val Asn Leu Leu Phe Pro Asp Pro Trp Leu Asn Ala
                115                 120                 125

GCT GAA AAT GGG GGT GAT ATT TTT AAG TCT CCG GCT ATG TCT CCA GAA      1031
Ala Glu Asn Gly Gly Asp Ile Phe Lys Ser Pro Ala Met Ser Pro Glu
            130                 135                 140

CCG TGG ATA GAT TTG TCT AGC TAC GAT AGC GAT GTA GAA GAG GTG ACT      1079
Pro Trp Ile Asp Leu Ser Ser Tyr Asp Ser Asp Val Glu Glu Val Thr
        145                 150                 155

AGT CAC TTT TTT CTG GAT TGC CCT GAA GAC CCC AGT CGG GAG TGT TCA      1127
Ser His Phe Phe Leu Asp Cys Pro Glu Asp Pro Ser Arg Glu Cys Ser
    160                 165                 170

TCT TGT GGG TTT CAT CAG GCT CAA AGC GGA ATT CCA GGC ATT ATG TGC      1175
Ser Cys Gly Phe His Gln Ala Gln Ser Gly Ile Pro Gly Ile Met Cys
175                 180                 185                 190

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Ser Leu Cys Tyr Met Arg Gln Thr Tyr His Cys Ile Tyr
                195                 200

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                                        Ser Pro Val Ser Glu Glu
                                            205

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Glu Met
210

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CTCTGCCAGG GAATGAAGCT TTTTTAAGGT TGCTTCGGAG CGGCTATTTT GAAGTGTTTG    1695
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CAGGTTTTCT CGTGGACCGT CTCTGCGTGC CGCTATGGCT GAAGGCCAGG GCGTTCAAGA 1875

TCACCCAGAG CTCCAGGAGC ACTTCGCAGC CTTCCTCGTC GCCCGACAAG ACGACCCAGA 1935

CTACCAGCCA GTAGACGGGG ACAGCCCACC CCGGGCTAGC CTGGAGGAGG CTGAACAGAG 1995

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TCTGGGAGGT TTGAAGAGGC GAATGGACTT GCTGGAAGAA TCTAATCAGC AGCTGCTGGC 3495

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GATGCATTCG GGGGCTAATA AGGTGGAGTT TAGCCTGAAT CTTAAGGTTG GCAATGTTGC 3975

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ATTTGGGGAA TTTATCATGA AGCTT 4060

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 211 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Lys Tyr Leu Val Leu Val Leu Asn Asp Gly Met Ser Arg Ile Glu
1 5 10 15

Lys Ala Leu Leu Cys Ser Asp Gly Glu Val Asp Leu Glu Cys His Glu
20 25 30

Val Leu Pro Pro Ser Pro Ala Pro Val Pro Ala Ser Val Ser Pro Val
35 40 45

Arg Ser Pro Pro Pro Leu Ser Pro Val Phe Pro Pro Ser Pro Pro Ala
50 55 60

Pro Leu Val Asn Pro Glu Ala Ser Ser Leu Leu Gln Gln Tyr Arg Arg
65 70 75 80

Glu Leu Leu Glu Arg Ser Leu Leu Arg Thr Ala Glu Gly Gln Gln Arg
85 90 95

Ala Val Cys Pro Cys Glu Arg Leu Pro Val Glu Glu Asp Glu Cys Leu
100 105 110

Asn Ala Val Asn Leu Leu Phe Pro Asp Pro Trp Leu Asn Ala Ala Glu
115 120 125

Asn Gly Gly Asp Ile Phe Lys Ser Pro Ala Met Ser Pro Glu Pro Trp
130 135 140

Ile Asp Leu Ser Ser Tyr Asp Ser Asp Val Glu Glu Val Thr Ser His
145 150 155 160

Phe Phe Leu Asp Cys Pro Glu Asp Pro Ser Arg Glu Cys Ser Ser Cys
165 170 175

Gly Phe His Gln Ala Gln Ser Gly Ile Pro Gly Ile Met Cys Ser Leu
180 185 190

Cys Tyr Met Arg Gln Thr Tyr His Cys Ile Tyr Ser Pro Val Ser Glu
195 200 205

Glu Glu Met
210

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4060 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1476..1946

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

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TTTTGGTGTT CGTACTTCCG TGTCACATAG TTCACTGTCA ATCTTCATTA CGGCTTAGAC    360

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CCACCATGAA GTACCTGGTC CTCGTTCTCA ACGACGGCAT GAGTCGAATT GAAAAAGCTC    660

TCCTGTGCAG CGATGGTGAG GTGGATTTAG AGTGTCATGA GGTACTTCCC CCTTCTCCCG    720

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CTCCGTCTCC GCCAGCCCCG CTTGTGAATC CAGAGGCGAG TTCGCTGCTG CAGCAGTATC    840

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                                       Met Asp His Leu Ser Val
                                         1               5

CTT TTG GAT TTG AAG CTG CTT CGC TCT ATC GTA GCG GGG GCT TCA AAT      1541
Leu Leu Asp Leu Lys Leu Leu Arg Ser Ile Val Ala Gly Ala Ser Asn
            10                  15                  20

CGC ACT GGA GTG TGG AAG AGG CGG CTG TGG CTG GGA CGC CTG ACT CAA      1589
Arg Thr Gly Val Trp Lys Arg Arg Leu Trp Leu Gly Arg Leu Thr Gln
        25                  30                  35

CTG GTC CAT GAT ACC TGC GTA GAG AAC GAG AGC ATA TTT CTC AAT TCT      1637
Leu Val His Asp Thr Cys Val Glu Asn Glu Ser Ile Phe Leu Asn Ser
    40                  45                  50

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Leu Pro Gly Asn Glu Ala Phe Leu Arg Leu Leu Arg Ser Gly Tyr Phe
55                  60                  65                  70

GAA GTG TTT GAC GTG TTT GTG GTG CCT GAG CTG CAT CTG GAC ACT CCG      1733
Glu Val Phe Asp Val Phe Val Val Pro Glu Leu His Leu Asp Thr Pro
                75                  80                  85

GGT CGA GTG GTC GCC GCT CTT GCT CTG CTG GTG TTC ATC CTC AAC GAT      1781
Gly Arg Val Val Ala Ala Leu Ala Leu Leu Val Phe Ile Leu Asn Asp
            90                  95                  100

TTA GAC GCT AAT TCT GCT TCT TCA GGC TTT GAT TCA GGT TTT CTC GTG      1829
Leu Asp Ala Asn Ser Ala Ser Ser Gly Phe Asp Ser Gly Phe Leu Val
        105                 110                 115

GAC CGT CTC TGC GTG CCG CTA TGG CTG AAG GCC AGG GCG TTC AAG ATC      1877
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Asp Arg Leu Cys Val Pro Leu Trp Leu Lys Ala Arg Ala Phe Lys Ile
    120                 125                 130

ACC CAG AGC TCC AGG AGC ACT TCG CAG CCT TCC TCG TCG CCC GAC AAG      1925
Thr Gln Ser Ser Arg Ser Thr Ser Gln Pro Ser Ser Ser Pro Asp Lys
135                 140                 145                 150

ACG ACC CAG ACT ACC AGC CAG TAGACGGGGA CAGCCCACCC CGGGCTAGCC        1976
Thr Thr Gln Thr Thr Ser Gln
                155

TGGAGGAGGC TGAACAGAGC AGCACTCGTT TCGAGCACAT CAGTTACCGA GACGTGGTGG   2036

ATGACTTCAA TAGATGCCAT GATGTTTTTT ATGAGAGGTA CAGTTTTGAG GACATAAAGA   2096

GCTACGAGGC TTTGCCTGAG GACAATTTGG AGCAGCTCAT AGCTATGCAT GCTAAAATCA   2156

AGCTGCTGCC CGGTCGGGAG TATGAGTTGA CTCAACCTTT GAACATAACA TCTTGCGCCT   2216

ATGTGCTCGG AAATGGGGCT ACTATTAGGG TAACAGGGGA AGCCTCCCCG GCTATTAGAG   2276

TGGGGGCCAT GGCCGTGGGT CCGTGTGTAA CAGGAATGAC TGGGGTGACT TTTGTGAATT   2336

GTAGGTTTGA GAGAGAGTCA ACAATTAGGG GGTCCCTGAT ACGAGCTTCA ACTCACGTGC   2396

TGTTTCATGG CTGTTATTTT ATGGGAATTA TGGGCACTTG TATTGAGGTG GGGGCGGGAG   2456

CTTACATTCG GGGTTGTGAG TTTGTGGGCT GTTACCGGGG AATCTGTTCT ACTTCTAACA   2516

GAGATATTAA GGTGAGGCAG TGCAACTTTG ACAAATGCTT ACTGGGTATT ACTTGTAAGG   2576

GGGACTATCG TCTTTCGGGA AATGTGTGTT CTGAGACTTT CTGCTTTGCT CATTTAGAGG   2636

GAGAGGGTTT GGTTAAAAAC AACACAGTCA AGTCCCCTAG TCGCTGGACC AGCGAGTCTG   2696

GCTTTTCCAT GATAACTTGT GCAGACGGCA GGGTTACGCC TTTGGGTTCC CTCCACATTG   2756

TGGGCAACCG TTGTAGGCGT TGGCCAACCA TGCAGGGGAA TGTGTTTATC ATGTCTAAAC   2816

TGTATCTGGG CAACAGAATA GGGACTGTAG CCCTGCCCCA GTGTGCTTTC TACAAGTCCA   2876

GCATTTGTTT GGAGGAGAGG GCGACAAACA AGCTGGTCTT GGCTTGTGCT TTTGAGAATA   2936

ATGTACTGGT GTACAAAGTG CTGAGACGGG AGAGTCCCTC AACCGTGAAA ATGTGTGTTT   2996

GTGGGACTTC TCATTATGCA AAGCCTTTGA CACTGGCAAT TATTTCTTCA GATATTCGGG   3056

CTAATCGATA CATGTACACT GTGGACTCAA CAGAGTTCAC TTCTGACGAG GATTAAAAGT   3116

GGGCGGGGCC AAGAGGGGTA TAAATAGGTG GGGAGGTTGA GGGGAGCCGT AGTTTCTGTT   3176

TTTCCCAGAC TGGGGGGGAC AACATGGCCG AGGAAGGGCG CATTTATGTG CCTTATGTAA   3236

CTGCCCGCCT GCCCAAGTGG TCGGGTTCGG TGCAGGATAA GACGGGCTCG AACATGTTGG   3296

GGGGTGTGGT ACTCCCTCCT AATTCACAGG CGCACCGGAC GGAGACCGTG GGCACTGAGG   3356

CCACCAGAGA CAACCTGCAC GCCGAGGGAG CGCGTCGTCC TGAGGATCAG ACGCCCTACA   3416

TGATCTTGGT GGAGGACTCT CTGGGAGGTT TGAAGAGGCG AATGGACTTG CTGGAAGAAT   3476

CTAATCAGCA GCTGCTGGCA ACTCTCAACC GTCTCCGTAC AGGACTCGCT GCCTATGTGC   3536

AGGCTAACCT TGTGGGCGGC CAAGTTAACC CCTTTGTTTA AATAAAAATA CACTCATACA   3596

GTTTATTATG CTGTCAATAA AATTCTTTAT TTTTCCTGTG ATAATACCGT GTCCAGCGTG   3656

CTCTGTCAAT AAGGGTCCTA TGCATCCTGA GAAGGGCCTC ATATACCCAT GGCATGAATA   3716

TTAAGATACA TGGGCATAAG GCCCTCAGAA GGGTTGAGGT AGAGCCACTG CAGACTTTCG   3776

TGGGGAGGTA AGGTGTTGTA AATAATCCAG TCATACTGAC TGTGCTGGGC GTGGAAGGAA   3836

AAGATGTCTT TTAGAAGAAG GGTGATTGGC AAAGGGAGGC TCTTAGTGTA GGTATTGATA   3896

AATCTGTTCA GTTGGGAGGG ATGCATTCGG GGGCTAATAA GGTGGAGTTT AGCCTGAATC   3956
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TTAAGGTTGG CAATGTTGCC CCCTAGGTCT TTGCGAGGAT TCATGTTGTG CAGTACCACA 4016

AAAACAGAGT AGCCTGTGCA TTTGGGGAAT TTATCATGAA GCTT 4060

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 157 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met Asp His Leu Ser Val Leu Leu Asp Leu Lys Leu Leu Arg Ser Ile
1 5 10 15

Val Ala Gly Ala Ser Asn Arg Thr Gly Val Trp Lys Arg Arg Leu Trp
20 25 30

Leu Gly Arg Leu Thr Gln Leu Val His Asp Thr Cys Val Glu Asn Glu
35 40 45

Ser Ile Phe Leu Asn Ser Leu Pro Gly Asn Glu Ala Phe Leu Arg Leu
50 55 60

Leu Arg Ser Gly Tyr Phe Glu Val Phe Asp Val Phe Val Val Pro Glu
65 70 75 80

Leu His Leu Asp Thr Pro Gly Arg Val Val Ala Ala Leu Ala Leu Leu
85 90 95

Val Phe Ile Leu Asn Asp Leu Asp Ala Asn Ser Ala Ser Ser Gly Phe
100 105 110

Asp Ser Gly Phe Leu Val Asp Arg Leu Cys Val Pro Leu Trp Leu Lys
115 120 125

Ala Arg Ala Phe Lys Ile Thr Gln Ser Ser Arg Ser Thr Ser Gln Pro
130 135 140

Ser Ser Ser Pro Asp Lys Thr Thr Gln Thr Thr Ser Gln
145 150 155

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4060 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1850..3109

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CATCATCAAT AATCTACAGT ACACTGATGG CAGCGGTCCA ACTGCCAATC ATTTTTGCCA 60

CGTCATTTAT GACGCAACGA CGGCGAGCGT GGCGTGCTGA CGTAACTGTG GGGCGGAGCG 120

CGTCGCGGAG GCGGCGGCGC TGGGCGGGGC TGAGGGCGGC GGGGGCGGCG CGCGGGGCGG 180

CGCGCGGGGC GGGGCGAGGG GCGGAGTTCC GCACCCGCTA CGTCATTTTC AGACATTTTT 240

TAGCAAATTT GCGCCTTTTG CAAGCATTTT TCTCACATTT CAGGTATTTA GAGGGCGGAT 300

TTTTGGTGTT CGTACTTCCG TGTCACATAG TTCACTGTCA ATCTTCATTA CGGCTTAGAC 360

AAATTTTCGG CGTCTTTTCC GGGTTTATGT CCCCGGTCAC CTTTATGACT GTGTGAAACA 420

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CACCTGCCCA TTGTTTACCC TTGGTCAGTT TTTTCGTCTC CTAGGGTGGG AACATCAAGA    480

ACAAATTTGC CGAGTAATTG TGCACCTTTT TCCGCGTTAG GACTGCGTTT CACACGTAGA    540

CAGACTTTTT CTCATTTTCT CACACTCCGT CGTCCGCTTC AGAGCTCTGC GTCTTCGCTG    600

CCACCATGAA GTACCTGGTC CTCGTTCTCA ACGACGGCAT GAGTCGAATT GAAAAAGCTC    660

TCCTGTGCAG CGATGGTGAG GTGGATTTAG AGTGTCATGA GGTACTTCCC CCTTCTCCCG    720

CGCCTGTCCC CGCTTCTGTG TCACCCGTGA GGAGTCCTCC TCCTCTGTCT CCGGTGTTTC    780

CTCCGTCTCC GCCAGCCCCG CTTGTGAATC CAGAGGCGAG TTCGCTGCTG CAGCAGTATC    840

GGAGAGAGCT GTTAGAGAGG AGCCTGCTCC GAACGGCCGA AGGTCAGCAG CGTGCAGTGT    900

GTCCATGTGA GCGGTTGCCC GTGGAAGAGG ATGAGTGTCT GAATGCCGTA AATTTGCTGT    960

TTCCTGATCC CTGGCTAAAT GCAGCTGAAA ATGGGGGTGA TATTTTTAAG TCTCCGGCTA   1020

TGTCTCCAGA ACCGTGGATA GATTTGTCTA GCTACGATAG CGATGTAGAA GAGGTGACTA   1080

GTCACTTTTT TCTGGATTGC CCTGAAGACC CCAGTCGGGA GTGTTCATCT TGTGGGTTTC   1140

ATCAGGCTCA AAGCGGAATT CCAGGCATTA TGTGCAGTTT GTGCTACATG CGCCAAACCT   1200

ACCATTGCAT CTATAGTAAG TACATTCTGT AAAAGAACAT CTTGGTGATT TCTAGGTATT   1260

GTTTAGGGAT TAACTGGGTG GAGTGATCTT AATCCGGCAT AACCAAATAC ATGTTTTCAC   1320

AGGTCCAGTT TCTGAAGAGG AAATGTGAGT CATGTTGACT TTGGCGCGCA AGAGGAAATG   1380

TGAGTCATGT TGACTTTGGC GCGCCCTACG GTGACTTTAA AGCAATTTGA GGATCACTTT   1440

TTTGTTAGTC GCTATAAAGT AGTCACGGAG TCTTCATGGA TCACTTAAGC GTTCTTTTGG   1500

ATTTGAAGCT GCTTCGCTCT ATCGTAGCGG GGGCTTCAAA TCGCACTGGA GTGTGGAAGA   1560

GGCGGCTGTG GCTGGGACGC CTGACTCAAC TGGTCCATGA TACCTGCGTA GAGAACGAGA   1620

GCATATTTCT CAATTCTCTG CCAGGGAATG AAGCTTTTTT AAGGTTGCTT CGGAGCGGCT   1680

ATTTTGAAGT GTTTGACGTG TTTGTGGTGC CTGAGCTGCA TCTGGACACT CCGGGTCGAG   1740

TGGTCGCCGC TCTTGCTCTG CTGGTGTTCA TCCTCAACGA TTTAGACGCT AATTCTGCTT   1800

CTTCAGGCTT TGATTCAGGT TTTCTCGTGG ACCGTCTCTG CGTGCCGCT ATG GCT       1855
                                                    Met Ala
                                                     1

GAA GGC CAG GGC GTT CAA GAT CAC CCA GAG CTC CAG GAG CAC TTC GCA      1903
Glu Gly Gln Gly Val Gln Asp His Pro Glu Leu Gln Glu His Phe Ala
     5                  10                  15

GCC TTC CTC GTC GCC CGA CAA GAC GAC CCA GAC TAC CAG CCA GTA GAC     1951
Ala Phe Leu Val Ala Arg Gln Asp Asp Pro Asp Tyr Gln Pro Val Asp
 20                  25                  30

GGG GAC AGC CCA CCC CGG GCT AGC CTG GAG GAG GCT GAA CAG AGC AGC     1999
Gly Asp Ser Pro Pro Arg Ala Ser Leu Glu Glu Ala Glu Gln Ser Ser
 35                  40                  45                  50

ACT CGT TTC GAG CAC ATC AGT TAC CGA GAC GTG GTG GAT GAC TTC AAT     2047
Thr Arg Phe Glu His Ile Ser Tyr Arg Asp Val Val Asp Asp Phe Asn
             55                  60                  65

AGA TGC CAT GAT GTT TTT TAT GAG AGG TAC AGT TTT GAG GAC ATA AAG     2095
Arg Cys His Asp Val Phe Tyr Glu Arg Tyr Ser Phe Glu Asp Ile Lys
         70                  75                  80

AGC TAC GAG GCT TTG CCT GAG GAC AAT TTG GAG CAG CTC ATA GCT ATG     2143
Ser Tyr Glu Ala Leu Pro Glu Asp Asn Leu Glu Gln Leu Ile Ala Met
     85                  90                  95

CAT GCT AAA ATC AAG CTG CTG CCC GGT CGG GAG TAT GAG TTG ACT CAA     2191
His Ala Lys Ile Lys Leu Leu Pro Gly Arg Glu Tyr Glu Leu Thr Gln
 100                 105                 110
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CCT TTG AAC ATA ACA TCT TGC GCC TAT GTG CTC GGA AAT GGG GCT ACT      2239
Pro Leu Asn Ile Thr Ser Cys Ala Tyr Val Leu Gly Asn Gly Ala Thr
115                 120                 125                 130

ATT AGG GTA ACA GGG GAA GCC TCC CCG GCT ATT AGA GTG GGG GCC ATG      2287
Ile Arg Val Thr Gly Glu Ala Ser Pro Ala Ile Arg Val Gly Ala Met
                135                 140                 145

GCC GTG GGT CCG TGT GTA ACA GGA ATG ACT GGG GTG ACT TTT GTG AAT      2335
Ala Val Gly Pro Cys Val Thr Gly Met Thr Gly Val Thr Phe Val Asn
            150                 155                 160

TGT AGG TTT GAG AGA GAG TCA ACA ATT AGG GGG TCC CTG ATA CGA GCT      2383
Cys Arg Phe Glu Arg Glu Ser Thr Ile Arg Gly Ser Leu Ile Arg Ala
        165                 170                 175

TCA ACT CAC GTG CTG TTT CAT GGC TGT TAT TTT ATG GGA ATT ATG GGC      2431
Ser Thr His Val Leu Phe His Gly Cys Tyr Phe Met Gly Ile Met Gly
    180                 185                 190

ACT TGT ATT GAG GTG GGG GCG GGA GCT TAC ATT CGG GGT TGT GAG TTT      2479
Thr Cys Ile Glu Val Gly Ala Gly Ala Tyr Ile Arg Gly Cys Glu Phe
195                 200                 205                 210

GTG GGC TGT TAC CGG GGA ATC TGT TCT ACT TCT AAC AGA GAT ATT AAG      2527
Val Gly Cys Tyr Arg Gly Ile Cys Ser Thr Ser Asn Arg Asp Ile Lys
                215                 220                 225

GTG AGG CAG TGC AAC TTT GAC AAA TGC TTA CTG GGT ATT ACT TGT AAG      2575
Val Arg Gln Cys Asn Phe Asp Lys Cys Leu Leu Gly Ile Thr Cys Lys
            230                 235                 240

GGG GAC TAT CGT CTT TCG GGA AAT GTG TGT TCT GAG ACT TTC TGC TTT      2623
Gly Asp Tyr Arg Leu Ser Gly Asn Val Cys Ser Glu Thr Phe Cys Phe
        245                 250                 255

GCT CAT TTA GAG GGA GAG GGT TTG GTT AAA AAC AAC ACA GTC AAG TCC      2671
Ala His Leu Glu Gly Glu Gly Leu Val Lys Asn Asn Thr Val Lys Ser
    260                 265                 270

CCT AGT CGC TGG ACC AGC GAG TCT GGC TTT TCC ATG ATA ACT TGT GCA      2719
Pro Ser Arg Trp Thr Ser Glu Ser Gly Phe Ser Met Ile Thr Cys Ala
275                 280                 285                 290

GAC GGC AGG GTT ACG CCT TTG GGT TCC CTC CAC ATT GTG GGC AAC CGT      2767
Asp Gly Arg Val Thr Pro Leu Gly Ser Leu His Ile Val Gly Asn Arg
                295                 300                 305

TGT AGG CGT TGG CCA ACC ATG CAG GGG AAT GTG TTT ATC ATG TCT AAA      2815
Cys Arg Arg Trp Pro Thr Met Gln Gly Asn Val Phe Ile Met Ser Lys
            310                 315                 320

CTG TAT CTG GGC AAC AGA ATA GGG ACT GTA GCC CTG CCC CAG TGT GCT      2863
Leu Tyr Leu Gly Asn Arg Ile Gly Thr Val Ala Leu Pro Gln Cys Ala
        325                 330                 335

TTC TAC AAG TCC AGC ATT TGT TTG GAG GAG AGG GCG ACA AAC AAG CTG      2911
Phe Tyr Lys Ser Ser Ile Cys Leu Glu Glu Arg Ala Thr Asn Lys Leu
    340                 345                 350

GTC TTG GCT TGT GCT TTT GAG AAT AAT GTA CTG GTG TAC AAA GTG CTG      2959
Val Leu Ala Cys Ala Phe Glu Asn Asn Val Leu Val Tyr Lys Val Leu
355                 360                 365                 370

AGA CGG GAG AGT CCC TCA ACC GTG AAA ATG TGT GTT TGT GGG ACT TCT      3007
Arg Arg Glu Ser Pro Ser Thr Val Lys Met Cys Val Cys Gly Thr Ser
                375                 380                 385

CAT TAT GCA AAG CCT TTG ACA CTG GCA ATT ATT TCT TCA GAT ATT CGG      3055
His Tyr Ala Lys Pro Leu Thr Leu Ala Ile Ile Ser Ser Asp Ile Arg
            390                 395                 400

GCT AAT CGA TAC ATG TAC ACT GTG GAC TCA ACA GAG TTC ACT TCT GAC      3103
Ala Asn Arg Tyr Met Tyr Thr Val Asp Ser Thr Glu Phe Thr Ser Asp
        405                 410                 415

GAG GAT TAAAAGTGGG CGGGGCCAAG AGGGGTATAA ATAGGTGGGG AGGTTGAGGG      3159
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Glu Asp
420

GAGCCGTAGT TTCTGTTTTT CCCAGACTGG GGGGGACAAC ATGGCCGAGG AAGGGCGCAT 3219

TTATGTGCCT TATGTAACTG CCCGCCTGCC CAAGTGGTCG GGTTCGGTGC AGGATAAGAC 3279

GGGCTCGAAC ATGTTGGGGG GTGTGGTACT CCCTCCTAAT TCACAGGCGC ACCGGACGGA 3339

GACCGTGGGC ACTGAGGCCA CCAGAGACAA CCTGCACGCC GAGGGAGCGC GTCGTCCTGA 3399

GGATCAGACG CCCTACATGA TCTTGGTGGA GGACTCTCTG GGAGGTTTGA AGAGGCGAAT 3459

GGACTTGCTG GAAGAATCTA ATCAGCAGCT GCTGGCAACT CTCAACCGTC TCCGTACAGG 3519

ACTCGCTGCC TATGTGCAGG CTAACCTTGT GGGCGGCCAA GTTAACCCCT TTGTTTAAAT 3579

AAAAATACAC TCATACAGTT TATTATGCTG TCAATAAAAT TCTTTATTTT TCCTGTGATA 3639

ATACCGTGTC CAGCGTGCTC TGTCAATAAG GGTCCTATGC ATCCTGAGAA GGGCCTCATA 3699

TACCCATGGC ATGAATATTA AGATACATGG GCATAAGGCC CTCAGAAGGG TTGAGGTAGA 3759

GCCACTGCAG ACTTTCGTGG GGAGGTAAGG TGTTGTAAAT AATCCAGTCA TACTGACTGT 3819

GCTGGGCGTG GAAGGAAAAG ATGTCTTTTA GAAGAAGGGT GATTGGCAAA GGGAGGCTCT 3879

TAGTGTAGGT ATTGATAAAT CTGTTCAGTT GGGAGGGATG CATTCGGGGG CTAATAAGGT 3939

GGAGTTTAGC CTGAATCTTA AGGTTGGCAA TGTTGCCCCC TAGGTCTTTG CGAGGATTCA 3999

TGTTGTGCAG TACCACAAAA ACAGAGTAGC CTGTGCATTT GGGGAATTTA TCATGAAGCT 4059

T 4060

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 420 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Met Ala Glu Gly Gln Gly Val Gln Asp His Pro Glu Leu Gln Glu His
1 5 10 15

Phe Ala Ala Phe Leu Val Ala Arg Gln Asp Asp Pro Asp Tyr Gln Pro
20 25 30

Val Asp Gly Asp Ser Pro Pro Arg Ala Ser Leu Glu Glu Ala Glu Gln
35 40 45

Ser Ser Thr Arg Phe Glu His Ile Ser Tyr Arg Asp Val Val Asp Asp
50 55 60

Phe Asn Arg Cys His Asp Val Phe Tyr Glu Arg Tyr Ser Phe Glu Asp
65 70 75 80

Ile Lys Ser Tyr Glu Ala Leu Pro Glu Asp Asn Leu Glu Gln Leu Ile
85 90 95

Ala Met His Ala Lys Ile Lys Leu Leu Pro Gly Arg Glu Tyr Glu Leu
100 105 110

Thr Gln Pro Leu Asn Ile Thr Ser Cys Ala Tyr Val Leu Gly Asn Gly
115 120 125

Ala Thr Ile Arg Val Thr Gly Glu Ala Ser Pro Ala Ile Arg Val Gly
130 135 140

Ala Met Ala Val Gly Pro Cys Val Thr Gly Met Thr Gly Val Thr Phe
145 150 155 160

Val Asn Cys Arg Phe Glu Arg Glu Ser Thr Ile Arg Gly Ser Leu Ile
165 170 175

Arg Ala Ser Thr His Val Leu Phe His Gly Cys Tyr Phe Met Gly Ile
180 185 190

Met Gly Thr Cys Ile Glu Val Gly Ala Gly Ala Tyr Ile Arg Gly Cys
195 200 205

Glu Phe Val Gly Cys Tyr Arg Gly Ile Cys Ser Thr Ser Asn Arg Asp
210 215 220

Ile Lys Val Arg Gln Cys Asn Phe Asp Lys Cys Leu Leu Gly Ile Thr
225 230 235 240

Cys Lys Gly Asp Tyr Arg Leu Ser Gly Asn Val Cys Ser Glu Thr Phe
245 250 255

Cys Phe Ala His Leu Glu Gly Glu Gly Leu Val Lys Asn Asn Thr Val
260 265 270

Lys Ser Pro Ser Arg Trp Thr Ser Glu Ser Gly Phe Ser Met Ile Thr
275 280 285

Cys Ala Asp Gly Arg Val Thr Pro Leu Gly Ser Leu His Ile Val Gly
290 295 300

Asn Arg Cys Arg Arg Trp Pro Thr Met Gln Gly Asn Val Phe Ile Met
305 310 315 320

Ser Lys Leu Tyr Leu Gly Asn Arg Ile Gly Thr Val Ala Leu Pro Gln
325 330 335

Cys Ala Phe Tyr Lys Ser Ser Ile Cys Leu Glu Glu Arg Ala Thr Asn
340 345 350

Lys Leu Val Leu Ala Cys Ala Phe Glu Asn Asn Val Leu Val Tyr Lys
355 360 365

Val Leu Arg Arg Glu Ser Pro Ser Thr Val Lys Met Cys Val Cys Gly
370 375 380

Thr Ser His Tyr Ala Lys Pro Leu Thr Leu Ala Ile Ile Ser Ser Asp
385 390 395 400

Ile Arg Ala Asn Arg Tyr Met Tyr Thr Val Asp Ser Thr Glu Phe Thr
405 410 415

Ser Asp Glu Asp
420

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4060 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 3200..3574

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CATCATCAAT AATCTACAGT ACACTGATGG CAGCGGTCCA ACTGCCAATC ATTTTTGCCA 60

CGTCATTTAT GACGCAACGA CGGCGAGCGT GGCGTGCTGA CGTAACTGTG GGGCGGAGCG 120

CGTCGCGGAG GCGGCGGCGC TGGGCGGGGC TGAGGGCGGC GGGGGCGGCG CGCGGGGCGG 180

CGCGCGGGGC GGGGCGAGGG GCGGAGTTCC GCACCCGCTA CGTCATTTTC AGACATTTTT 240

TAGCAAATTT GCGCCTTTTG CAAGCATTTT TCTCACATTT CAGGTATTTA GAGGGCGGAT 300

TTTTGGTGTT CGTACTTCCG TGTCACATAG TTCACTGTCA ATCTTCATTA CGGCTTAGAC 360

AAATTTTCGG CGTCTTTTCC GGGTTTATGT CCCCGGTCAC CTTTATGACT GTGTGAAACA 420

CACCTGCCCA TTGTTTACCC TTGGTCAGTT TTTTCGTCTC CTAGGGTGGG AACATCAAGA 480

ACAAATTTGC CGAGTAATTG TGCACCTTTT TCCGCGTTAG GACTGCGTTT CACACGTAGA 540

CAGACTTTTT CTCATTTTCT CACACTCCGT CGTCCGCTTC AGAGCTCTGC GTCTTCGCTG 600

CCACCATGAA GTACCTGGTC CTCGTTCTCA ACGACGGCAT GAGTCGAATT GAAAAAGCTC 660

TCCTGTGCAG CGATGGTGAG GTGGATTTAG AGTGTCATGA GGTACTTCCC CCTTCTCCCG 720

CGCCTGTCCC CGCTTCTGTG TCACCCGTGA GGAGTCCTCC TCCTCTGTCT CCGGTGTTTC 780

CTCCGTCTCC GCCAGCCCCG CTTGTGAATC CAGAGGCGAG TTCGCTGCTG CAGCAGTATC 840

GGAGAGAGCT GTTAGAGAGG AGCCTGCTCC GAACGGCCGA AGGTCAGCAG CGTGCAGTGT 900

GTCCATGTGA GCGGTTGCCC GTGGAAGAGG ATGAGTGTCT GAATGCCGTA AATTTGCTGT 960

TTCCTGATCC CTGGCTAAAT GCAGCTGAAA ATGGGGGTGA TATTTTTAAG TCTCCGGCTA 1020

TGTCTCCAGA ACCGTGGATA GATTTGTCTA GCTACGATAG CGATGTAGAA GAGGTGACTA 1080

GTCACTTTTT TCTGGATTGC CCTGAAGACC CCAGTCGGGA GTGTTCATCT TGTGGGTTTC 1140

ATCAGGCTCA AAGCGGAATT CCAGGCATTA TGTGCAGTTT GTGCTACATG CGCCAAACCT 1200

ACCATTGCAT CTATAGTAAG TACATTCTGT AAAAGAACAT CTTGGTGATT TCTAGGTATT 1260

GTTTAGGGAT TAACTGGGTG GAGTGATCTT AATCCGGCAT AACCAAATAC ATGTTTTCAC 1320

AGGTCCAGTT TCTGAAGAGG AAATGTGAGT CATGTTGACT TTGGCGCGCA AGAGGAAATG 1380

TGAGTCATGT TGACTTTGGC GCGCCCTACG GTGACTTTAA AGCAATTTGA GGATCACTTT 1440

TTTGTTAGTC GCTATAAAGT AGTCACGGAG TCTTCATGGA TCACTTAAGC GTTCTTTTGG 1500

ATTTGAAGCT GCTTCGCTCT ATCGTAGCGG GGGCTTCAAA TCGCACTGGA GTGTGGAAGA 1560

GGCGGCTGTG GCTGGGACGC CTGACTCAAC TGGTCCATGA TACCTGCGTA GAGAACGAGA 1620

GCATATTTCT CAATTCTCTG CCAGGGAATG AAGCTTTTTT AAGGTTGCTT CGGAGCGGCT 1680

ATTTTGAAGT GTTTGACGTG TTTGTGGTGC CTGAGCTGCA TCTGGACACT CCGGGTCGAG 1740

TGGTCGCCGC TCTTGCTCTG CTGGTGTTCA TCCTCAACGA TTTAGACGCT AATTCTGCTT 1800

CTTCAGGCTT TGATTCAGGT TTTCTCGTGG ACCGTCTCTG CGTGCCGCTA TGGCTGAAGG 1860

CCAGGGCGTT CAAGATCACC CAGAGCTCCA GGAGCACTTC GCAGCCTTCC TCGTCGCCCG 1920

ACAAGACGAC CCAGACTACC AGCCAGTAGA CGGGGACAGC CCACCCCGGG CTAGCCTGGA 1980

GGAGGCTGAA CAGAGCAGCA CTCGTTTCGA GCACATCAGT TACCGAGACG TGGTGGATGA 2040

CTTCAATAGA TGCCATGATG TTTTTTATGA GAGGTACAGT TTTGAGGACA TAAAGAGCTA 2100

CGAGGCTTTG CCTGAGGACA ATTTGGAGCA GCTCATAGCT ATGCATGCTA AAATCAAGCT 2160

GCTGCCCGGT CGGGAGTATG AGTTGACTCA ACCTTTGAAC ATAACATCTT GCGCCTATGT 2220

GCTCGGAAAT GGGGCTACTA TTAGGGTAAC AGGGGAAGCC TCCCCGGCTA TTAGAGTGGG 2280

GGCCATGGCC GTGGGTCCGT GTGTAACAGG AATGACTGGG GTGACTTTTG TGAATTGTAG 2340

GTTTGAGAGA GAGTCAACAA TTAGGGGGTC CCTGATACGA GCTTCAACTC ACGTGCTGTT 2400

TCATGGCTGT TATTTTATGG GAATTATGGG CACTTGTATT GAGGTGGGGG CGGGAGCTTA 2460

CATTCGGGGT TGTGAGTTTG TGGGCTGTTA CCGGGGAATC TGTTCTACTT CTAACAGAGA 2520

TATTAAGGTG AGGCAGTGCA ACTTTGACAA ATGCTTACTG GGTATTACTT GTAAGGGGGA 2580

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CTATCGTCTT TCGGGAAATG TGTGTTCTGA GACTTTCTGC TTTGCTCATT TAGAGGGAGA   2640

GGGTTTGGTT AAAAACAACA CAGTCAAGTC CCCTAGTCGC TGGACCAGCG AGTCTGGCTT   2700

TTCCATGATA ACTTGTGCAG ACGGCAGGGT TACGCCTTTG GGTTCCCTCC ACATTGTGGG   2760

CAACCGTTGT AGGCGTTGGC CAACCATGCA GGGGAATGTG TTTATCATGT CTAAACTGTA   2820

TCTGGGCAAC AGAATAGGGA CTGTAGCCCT GCCCCAGTGT GCTTTCTACA AGTCCAGCAT   2880

TTGTTTGGAG GAGAGGGCGA CAAACAAGCT GGTCTTGGCT TGTGCTTTTG AGAATAATGT   2940

ACTGGTGTAC AAAGTGCTGA GACGGGAGAG TCCCTCAACC GTGAAAATGT GTGTTTGTGG   3000

GACTTCTCAT TATGCAAAGC CTTTGACACT GGCAATTATT TCTTCAGATA TTCGGGCTAA   3060

TCGATACATG TACACTGTGG ACTCAACAGA GTTCACTTCT GACGAGGATT AAAAGTGGGC   3120

GGGGCCAAGA GGGGTATAAA TAGGTGGGGA GGTTGAGGGG AGCCGTAGTT TCTGTTTTTC   3180

CCAGACTGGG GGGGACAAC ATG GCC GAG GAA GGG CGC ATT TAT GTG CCT TAT      3232
                     Met Ala Glu Glu Gly Arg Ile Tyr Val Pro Tyr
                       1               5                  10

GTA ACT GCC CGC CTG CCC AAG TGG TCG GGT TCG GTG CAG GAT AAG ACG      3280
Val Thr Ala Arg Leu Pro Lys Trp Ser Gly Ser Val Gln Asp Lys Thr
            15                  20                  25

GGC TCG AAC ATG TTG GGG GGT GTG GTA CTC CCT CCT AAT TCA CAG GCG      3328
Gly Ser Asn Met Leu Gly Gly Val Val Leu Pro Pro Asn Ser Gln Ala
        30                  35                  40

CAC CGG ACG GAG ACC GTG GGC ACT GAG GCC ACC AGA GAC AAC CTG CAC      3376
His Arg Thr Glu Thr Val Gly Thr Glu Ala Thr Arg Asp Asn Leu His
    45                  50                  55

GCC GAG GGA GCG CGT CGT CCT GAG GAT CAG ACG CCC TAC ATG ATC TTG      3424
Ala Glu Gly Ala Arg Arg Pro Glu Asp Gln Thr Pro Tyr Met Ile Leu
60                  65                  70                  75

GTG GAG GAC TCT CTG GGA GGT TTG AAG AGG CGA ATG GAC TTG CTG GAA      3472
Val Glu Asp Ser Leu Gly Gly Leu Lys Arg Arg Met Asp Leu Leu Glu
                80                  85                  90

GAA TCT AAT CAG CAG CTG CTG GCA ACT CTC AAC CGT CTC CGT ACA GGA      3520
Glu Ser Asn Gln Gln Leu Leu Ala Thr Leu Asn Arg Leu Arg Thr Gly
            95                  100                 105

CTC GCT GCC TAT GTG CAG GCT AAC CTT GTG GGC GGC CAA GTT AAC CCC      3568
Leu Ala Ala Tyr Val Gln Ala Asn Leu Val Gly Gly Gln Val Asn Pro
        110                 115                 120

TTT GTT TAAATAAAAA TACACTCATA CAGTTTATTA TGCTGTCAAT AAAATTCTTT       3624
Phe Val
    125

ATTTTTCCTG TGATAATACC GTGTCCAGCG TGCTCTGTCA ATAAGGGTCC TATGCATCCT   3684

GAGAAGGGCC TCATATACCC ATGGCATGAA TATTAAGATA CATGGGCATA AGGCCCTCAG   3744

AAGGGTTGAG GTAGAGCCAC TGCAGACTTT CGTGGGGAGG TAAGGTGTTG TAAATAATCC   3804

AGTCATACTG ACTGTGCTGG GCGTGGAAGG AAAAGATGTC TTTTAGAAGA AGGGTGATTG   3864

GCAAAGGGAG GCTCTTAGTG TAGGTATTGA TAAATCTGTT CAGTTGGGAG GGATGCATTC   3924

GGGGGCTAAT AAGGTGGAGT TTAGCCTGAA TCTTAAGGTT GGCAATGTTG CCCCCTAGGT   3984

CTTTGCGAGG ATTCATGTTG TGCAGTACCA CAAAAACAGA GTAGCCTGTG CATTTGGGGA   4044

ATTTATCATG AAGCTT                                                   4060
```

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 125 amino acids

(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Met Ala Glu Glu Gly Arg Ile Tyr Val Pro Tyr Val Thr Ala Arg Leu
1 5 10 15

Pro Lys Trp Ser Gly Ser Val Gln Asp Lys Thr Gly Ser Asn Met Leu
20 25 30

Gly Gly Val Val Leu Pro Pro Asn Ser Gln Ala His Arg Thr Glu Thr
35 40 45

Val Gly Thr Glu Ala Thr Arg Asp Asn Leu His Ala Glu Gly Ala Arg
50 55 60

Arg Pro Glu Asp Gln Thr Pro Tyr Met Ile Leu Val Glu Asp Ser Leu
65 70 75 80

Gly Gly Leu Lys Arg Arg Met Asp Leu Leu Glu Glu Ser Asn Gln Gln
85 90 95

Leu Leu Ala Thr Leu Asn Arg Leu Arg Thr Gly Leu Ala Ala Tyr Val
100 105 110

Gln Ala Asn Leu Val Gly Gly Gln Val Asn Pro Phe Val
115 120 125

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 54 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Glu Glu Phe Val Leu Asp Tyr Val Glu His Pro Gly His Gly Cys Arg
1 5 10 15

Ser Cys His Tyr His Arg Arg Asn Thr Gly Asp Pro Asp Ile Met Cys
20 25 30

Ser Leu Cys Tyr Met Arg Thr Cys Gly Met Phe Val Tyr Ser Pro Val
35 40 45

Ser Glu Pro Glu Pro Glu
50

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Ile Asp Leu Thr Cys His Glu Ala Gly Phe Pro Pro Ser
1 5 10

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Leu Asp Phe Ser Thr Pro Gly Arg Ala Ala Ala Ala Val Ala Phe Leu
1 5 10 15

Ser Phe Ile

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Gln Ser Ser Asn Ser Thr Ser
1 5

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 347 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Gln Lys Tyr Ser Ile Glu Gln Leu Thr Thr Tyr Trp Leu Gln Pro Gly
1 5 10 15

Asp Asp Phe Glu Glu Ala Ile Arg Val Tyr Ala Lys Val Ala Leu Arg
20 25 30

Pro Asp Cys Lys Tyr Lys Ile Ser Lys Leu Val Asn Ile Arg Asn Cys
35 40 45

Cys Tyr Ile Ser Gly Asn Gly Ala Glu Val Glu Ile Asp Thr Glu Asp
50 55 60

Arg Val Ala Phe Arg Cys Ser Met Ile Asn Met Trp Pro Gly Val Leu
65 70 75 80

Gly Met Asp Gly Val Val Ile Met Asn Val Arg Phe Thr Gly Pro Asn
85 90 95

Phe Ser Gly Thr Val Phe Leu Ala Asn Thr Asn Leu Ile Leu His Gly
100 105 110

Val Ser Phe Tyr Gly Phe Asn Asn Thr Cys Val Glu Ala Trp Thr Asp
115 120 125

Val Arg Val Arg Gly Cys Ala Phe Tyr Cys Cys Trp Lys Gly Val Val
130 135 140

Cys Arg Pro Lys Ser Arg Ala Ser Ile Lys Lys Cys Leu Phe Glu Arg
145 150 155 160

Cys Thr Leu Gly Ile Leu Ser Glu Gly Asn Ser Arg Val Arg His Asn
165 170 175

Val Ala Ser Asp Cys Gly Cys Phe Met Leu Val Lys Ser Val Ala Val
180 185 190

Ile Lys His Asn Met Val Cys Gly Asn Cys Glu Asp Arg Ala Ser Gln
195 200 205

Met Leu Thr Cys Ser Asp Gly Asn Cys His Leu Leu Lys Thr Ile His
210 215 220

Val Ala Ser His Ser Arg Lys Ala Trp Pro Val Phe Glu His Asn Ile
225 230 235 240

Leu His Arg Cys Ser Leu His Leu Gly Asn Arg Arg Gly Val Phe Leu
245 250 255

Pro Tyr Gln Cys Asn Leu Ser His Thr Lys Ile Leu Leu Glu Pro Glu
260 265 270

Ser Met Ser Lys Val Asn Leu Asn Gly Val Phe Asp Met Thr Met Lys
275 280 285

Ile Trp Lys Val Leu Arg Tyr Asp Glu Thr Arg Thr Arg Cys Arg Pro
290 295 300

Cys Glu Cys Gly Gly Lys His Ile Arg Asn Gln Pro Val Met Leu Asp
305 310 315 320

Val Thr Glu Glu Leu Arg Pro Asp His Leu Val Leu Ala Cys His Arg
325 330 335

Ala Glu Phe Gly Ser Ser Asp Glu Asp Thr Asp
340 345

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 140 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Met Ser Thr Asn Ser Phe Asp Gly Ser Ile Val Ser Ser Tyr Leu Thr
1 5 10 15

Thr Arg Met Pro Pro Trp Ala Gly Val Arg Gln Asn Val Met Gly Ser
20 25 30

Ser Ile Asp Gly Arg Pro Val Leu Pro Ala Asn Ser Thr Thr Leu Thr
35 40 45

Tyr Glu Thr Val Ser Gly Thr Pro Leu Glu Thr Ala Ala Ser Ala Ala
50 55 60

Ala Ser Ala Ala Ala Ala Thr Ala Arg Gly Ile Val Thr Asp Phe Ala
65 70 75 80

Phe Leu Ser Pro Leu Ala Ser Ser Ala Ala Ser Arg Ser Ser Ala Arg
85 90 95

Asp Asp Lys Leu Thr Ala Leu Leu Ala Gln Leu Asp Ser Leu Thr Arg
100 105 110

Glu Leu Asn Val Val Ser Gln Gln Leu Leu Asp Leu Arg Gln Gln Val
115 120 125

Ser Ala Leu Lys Ala Ser Ser Pro Pro Asn Ala Val
130 135 140

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5100 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..418

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

```
C CTC ATC AAA CAA CCC GTG GTG GGC ACC ACC CAC GTG GAA ATG CCT          46
  Leu Ile Lys Gln Pro Val Val Gly Thr Thr His Val Glu Met Pro
    1               5                  10                  15

CGC AAC GAA GTC CTA GAA CAA CAT CTG ACC TCA CAT GGC GCT CAA ATC          94
Arg Asn Glu Val Leu Glu Gln His Leu Thr Ser His Gly Ala Gln Ile
                20                  25                  30

GCG GGC GGA GGC GCT GCG GGC GAT TAC TTT AAA AGC CCC ACT TCA GCT         142
Ala Gly Gly Gly Ala Ala Gly Asp Tyr Phe Lys Ser Pro Thr Ser Ala
            35                  40                  45

CGA ACC CTT ATC CCG CTC ACC GCC TCC TGC TTA AGA CCA GAT GGA GTC         190
Arg Thr Leu Ile Pro Leu Thr Ala Ser Cys Leu Arg Pro Asp Gly Val
        50                  55                  60

TTT CAA CTA GGA GGA GGC TCG CGT TCA TCT TTC AAC CCC CTG CAA ACA         238
Phe Gln Leu Gly Gly Gly Ser Arg Ser Ser Phe Asn Pro Leu Gln Thr
    65                  70                  75

GAT TTT GCC TTC CAC GCC CTG CCC TCC AGA CCG CGC CAC GGG GGC ATA         286
Asp Phe Ala Phe His Ala Leu Pro Ser Arg Pro Arg His Gly Gly Ile
80                  85                  90                  95

GGA TCC AGG CAG TTT GTA GAG GAA TTT GTG CCC GCC GTC TAC CTC AAC         334
Gly Ser Arg Gln Phe Val Glu Glu Phe Val Pro Ala Val Tyr Leu Asn
                100                 105                 110

CCC TAC TCG GGA CCG CCG GAC TCT TAT CCG GAC CAG TTT ATA CGC CAC         382
Pro Tyr Ser Gly Pro Pro Asp Ser Tyr Pro Asp Gln Phe Ile Arg His
            115                 120                 125

TAC AAC GTG TAC AGC AAC TCT GTG AGC GGT TAT AGC TGAGATTGTA              428
Tyr Asn Val Tyr Ser Asn Ser Val Ser Gly Tyr Ser
        130                 135

AGACTCTCCT ATCTGTCTCT GTGCTGCTTT TCCGCTTCAA GCCCCACAAG CATGAAGGGG       488

TTTCTGCTCA TCTTCAGCCT GCTTGTGCAT TGTCCCCTAA TTCATGTTGG GACCATTAGC       548

TTCTATGCTG CAAGGCCCGG GTCTGAGCCT AACGCGACTT ATGTTTGTGA CTATGGAAGC       608

GAGTCAGATT ACAACCCCAC CACGGTTCTG TGGTTGGCTC GAGAGACCGA TGGCTCCTGG       668

ATCTCTGTTC TTTTCCGTCA CAACGGCTCC TCAACTGCAG CCCCCGGGGT CGTCGCGCAC       728

TTTACTGACC ACAACAGCAG CATTGTGGTG CCCCAGTATT ACCTCCTCAA CAACTCACTC       788

TCTAAGCTCT GCTGCTCATA CCGGCACAAC GAGCGTTCTC AGTTTACCTG CAAACAAGCT       848

GACGTCCCTA CCTGTCACGA GCCCGGCAAG CCGCTCACCC TCCGCGTCTC CCCCGCGCTG       908

GGAACTGCCC ACCAAGCAGT CACTTGGTTT TTTCAAAATG TACCCATAGC TACTGTTTAC       968

CGACCTTGGG GCAATGTAAC TTGGTTTTGT CCTCCCTTCA TGTGTACCTT TAATGTCAGC      1028

CTGAACTCCC TACTTATTTA CAACTTTTCT GACAAAACCG GGGGGCAATA CACAGCTCTC      1088

ATGCACTCCG GACCTGCTTC CCTCTTTCAG CTCTTTAAGC CAACGACTTG TGTCACCAAG      1148
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GTGGAGGACC CGCCGTATGC CAACGACCCG GCCTCGCCTG TGTGGCGCCC ACTGCTTTTT 1208

GCCTTCGTCC TCTGCACCGG CTGCGCGGTG TTGTTAACCG CCTTCGGTCC ATCGATTCTA 1268

TCCGGTACCC GAAAGCTTAT CTCAGCCCGC TTTTGGAGTC CCGAGCCCTA TACCACCCTC 1328

CACTAACAGT CCCCCCATGG AGCCAGACGG AGTTCATGCC GAGCAGCAGT TTATCCTCAA 1388

TCAGATTTCC TGCGCCAACA CTGCCCTCCA GCGTCAAAGG GAGGAACTAG CTTCCCTTGT 1448

CATGTTGCAT GCCTGTAAGC GTGGCCTCTT TTGTCCAGTC AAAACTTACA AGCTCAGCCT 1508

CAACGCCTCG GCCAGCGAGC ACAGCCTGCA CTTTGAAAAA AGTCCCTCCC GATTCACCCT 1568

GGTCAACACT CACGCCGGAG CTTCTGTGCG AGTGGCCCTA CACCACCAGG GAGCTTCCGG 1628

CAGCATCCGC TGTTCCTGTT CCCACGCCGA GTGCCTCCCC GTCCTCCTCA AGACCCTCTG 1688

TGCCTTTAAC TTTTTAGATT AGCTGAAAGC AAATATAAAA TGGTGTGCTT ACCGTAATTC 1748

TGTTTTGACT TGTGTGCTTG ATTTCTCCCC CTGCGCCGTA ATCCAGTGCC CCTCTTCAAA 1808

ACTCTCGTAC CCTATGCGAT TCGCATAGGC ATATTTTCTA AAAGCTCTGA AGTCAACATC 1868

ACTCTCAAAC ACTTCTCCGT TGTAGGTTAC TTTCATCTAC AGATAAAGTC ATCCACCGGT 1928

TAACATCATG AAGAGAAGTG TGCCCCAGGA CTTTAATCTT GTGTATCCGT ACAAGGCTAA 1988

GAGGCCCAAC ATCATGCCGC CCTTTTTTGA CCGCAATGGC TTTGTTGAAA ACCAAGAAGC 2048

CACGCTAGCC ATGCTTGTGG AAAAGCCGCT CACGTTCGAC AAGGAAGGTG CGCTGACCCT 2108

GGGCGTCGGA CGCGGCATCC GCATTAACCC CGCGGGGCTT CTGGAGACAA ACGACCTCGC 2168

GTCCGCTGTC TTCCCACCGC TGGCCTCCGA TGAGGCCGGC AACGTCACGC TCAACATGTC 2228

TGACGGGCTA TATACTAAGG ACAACAAGCT AGCTGTCAAA GTAGGTCCCG GGCTGTCCCT 2288

CGACTCCAAT AATGCTCTCC AGGTCCACAC AGGCGACGGG CTCACGGTAA CCGATGACAA 2348

GGTGTCTCTA AATACCCAAG CTCCCCTCTC GACCACCAGC GCGGGCCTCT CCCTACTTCT 2408

GGGTCCCAGC CTCCACTTAG GTGAGGAGGA ACGACTAACA GTAAACACCG GAGCGGGCCT 2468

CCAAATTAGC AATAACGCTC TGGCCGTAAA AGTAGGTTCA GGTATCACCG TAGATGCTCA 2528

AAACCAGCTC GCTGCATCCC TGGGGGACGG TCTAGAAAGC AGAGATAATA AAACTGTCGT 2588

TAAGGCTGGG CCCGGACTTA CAATAACTAA TCAAGCTCTT ACTGTTGCTA CCGGGAACGG 2648

CCTTCAGGTC AACCCGGAAG GGCAACTGCA GCTAAACATT ACTGCCGGTC AGGGCCTCAA 2708

CTTTGCAAAC AACAGCCTCG CCGTGGAGCT GGGCTCGGGC CTGCATTTTC CCCCTGGCCA 2768

AAACCAAGTA AGCCTTTATC CCGGAGATGG AATAGACATC CGAGATAATA GGGTGACTGT 2828

GCCCGCTGGG CCAGGCCTGA GAATGCTCAA CCACCAACTT GCCGTAGCTT CCGGAGACGG 2888

TTTAGAAGTC CACAGCGACA CCCTCCGGTT AAAGCTCTCC CACGGCCTGA CATTTGAAAA 2948

TGGCGCCGTA CGAGCAAAAC TAGGACCAGG ACTTGGCACA GACGACTCTG GTCGGTCCGT 3008

GGTTCGCACA GGTCGAGGAC TTAGAGTTGC AAACGGCCAA GTCCAGATCT TCAGCGGAAG 3068

AGGCACCGCC ATCGGCACTG ATAGCAGCCT CACTCTCAAC ATCCGGGCGC CCCTACAATT 3128

TTCTGGACCC GCCTTGACTG CTAGTTTGCA AGGCAGTGGT CCGATTACTT ACAACAGCAA 3188

CAATGGCACT TTCGGTCTCT CTATAGGCCC CGGAATGTGG GTAGACCAAA ACAGACTTCA 3248

GGTAAACCCA GGCGCTGGTT TAGTCTTCCA AGGAAACAAC CTTGTCCCAA ACCTTGCGGA 3308

TCCGCTGGCT ATTTCCGACA GCAAAATTAG TCTCAGTCTC GGTCCCGGCC TGACCCAAGC 3368

TTCCAACGCC CTGACTTTAA GTTTAGGAAA CGGGCTTGAA TTCTCCAATC AAGCCGTTGC 3428

TATAAAAGCG GGCCGGGGCT TACGCTTTGA GTCTTCCTCA CAAGCTTTAG AGAGCAGCCT 3488

CACAGTCGGA AATGGCTTAA CGCTTACCGA TACTGTGATC CGCCCCAACC TAGGGGACGG 3548

CCTAGAGGTC AGAGACAATA AAATCATTGT TAAGCTGGGC GCGAATCTTC GTTTTGAAAA 3608

CGGAGCCGTA ACCGCCGGCA CCGTTAACCC TTCTGCGCCC GAGGCACCAC CAACTCTCAC 3668

TGCAGAACCA CCCCTCCGAG CCTCCAACTC CCATCTTCAA CTGTCCCTAT CGGAGGGCTT 3728

GGTTGTGCAT AACAACGCCC TTGCTCTCCA ACTGGGAGAC GGCATGGAAG TAAATCAGCA 3788

CGGACTTACT TTAAGAGTAG GCTCGGGTTT GCAAATGCGT GACGGCATTT TAACAGTTAC 3848

ACCCAGCGGC ACTCCTATTG AGCCCAGACT GACTGCCCCA CTGACTCAGA CAGAGAATGG 3908

AATCGGGCTC GCTCTCGGCG CCGGCTTGGA ATTAGACGAG AGCGCGCTCC AAGTAAAAGT 3968

TGGGCCCGGC ATGCGCCTGA ACCCTGTAGA AAAGTATGTA ACCCTGCTCC TGGGTCCTGG 4028

CCTTAGTTTT GGGCAGCCGG CCAACAGGAC AAATTATGAT GTGCGCGTTT CTGTGGAGCC 4088

CCCCATGGTT TTCGGACAGC GTGGTCAGCT CACATTTTTA GTGGGTCACG GACTACACAT 4148

TCAAAATTCC AAACTTCAGC TCAATTTGGG ACAAGGCCTC AGAACTGACC CCGTCACCAA 4208

CCAGCTGGAA GTGCCCCTCG GTCAAGGTTT GGAAATTGCA GACGAATCCC AGGTTAGGGT 4268

TAAATTGGGC GATGGCCTGC AGTTTGATTC ACAAGCTCGC ATCACTACCG CTCCTAACAT 4328

GGTCACTGAA ACTCTGTGGA CCGGAACAGG CAGTAATGCT AATGTTACAT GGCGGGGCTA 4388

CACTGCCCCC GGCAGCAAAC TCTTTTTGAG TCTCACTCGG TTCAGCACTG GTCTAGTTTT 4448

AGGAAACATG ACTATTGACA GCAATGCATC CTTTGGGCAA TACATTAACG CGGGACACGA 4508

ACAGATCGAA TGCTTTATAT TGTTGGACAA TCAGGGTAAC CTAAAAGAAG GATCTAACTT 4568

GCAAGGCACT TGGGAAGTGA AGAACAACCC CTCTGCTTCC AAAGCTGCTT TTTTGCCTTC 4628

CACCGCCCTA TACCCCATCC TCAACGAAAG CCGAGGGAGT CTTCCTGGAA AAAATCTTGT 4688

GGGCATGCAA GCCATACTGG GAGGCGGGGG CACTTGCACT GTGATAGCCA CCCTCAATGG 4748

CAGACGCAGC AACAACTATC CCGCGGGCCA GTCCATAATT TTCGTGTGGC AAGAATTCAA 4808

CACCATAGCC CGCCAACCTC TGAACCACTC TACACTTACT TTTTCTTACT GGACTTAAAT 4868

AAGTTGGAAA TAAAGAGTTA AACTGAATGT TTAAGTGCAA CAGACTTTTA TTGGTTTTGG 4928

CTCACAACAA ATTACAACAG CATAGACAAG TCATACCGGT CAAACAACAC AGGCTCTCGA 4988

AAACGGGCTA ACCGCTCCAA GAATCTGTCA CGCAGACGAG CAAGTCCTAA ATGTTTTTTC 5048

ACTCTCTTCG GGGCCAAGTT CAGCATGTAT CGGATTTTCT GCTTACACCT TT 5100

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 139 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Leu Ile Lys Gln Pro Val Val Gly Thr Thr His Val Glu Met Pro Arg
1 5 10 15

Asn Glu Val Leu Glu Gln His Leu Thr Ser His Gly Ala Gln Ile Ala
20 25 30

Gly Gly Gly Ala Ala Gly Asp Tyr Phe Lys Ser Pro Thr Ser Ala Arg
35 40 45

Thr Leu Ile Pro Leu Thr Ala Ser Cys Leu Arg Pro Asp Gly Val Phe
50 55 60

Gln Leu Gly Gly Gly Ser Arg Ser Ser Phe Asn Pro Leu Gln Thr Asp
65 70 75 80

Phe Ala Phe His Ala Leu Pro Ser Arg Pro Arg His Gly Gly Ile Gly
85 90 95

Ser Arg Gln Phe Val Glu Glu Phe Val Pro Ala Val Tyr Leu Asn Pro
100 105 110

Tyr Ser Gly Pro Pro Asp Ser Tyr Pro Asp Gln Phe Ile Arg His Tyr
115 120 125

Asn Val Tyr Ser Asn Ser Val Ser Gly Tyr Ser
130 135

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5100 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 408..1331

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

CCTCATCAAA CAACCCGTGG TGGGCACCAC CCACGTGGAA ATGCCTCGCA ACGAAGTCCT 60

AGAACAACAT CTGACCTCAC ATGGCGCTCA AATCGCGGGC GGAGGCGCTG CGGGCGATTA 120

CTTTAAAAGC CCCACTTCAG CTCGAACCCT TATCCCGCTC ACCGCCTCCT GCTTAAGACC 180

AGATGGAGTC TTTCAACTAG GAGGAGGCTC GCGTTCATCT TTCAACCCCC TGCAAACAGA 240

TTTTGCCTTC CACGCCCTGC CCTCCAGACC GCGCCACGGG GGCATAGGAT CCAGGCAGTT 300

TGTAGAGGAA TTTGTGCCCG CCGTCTACCT CAACCCCTAC TCGGGACCGC CGGACTCTTA 360

TCCGGACCAG TTTATACGCC ACTACAACGT GTACAGCAAC TCTGTGA GCG GTT ATA 416
Ala Val Ile
1

GCT GAG ATT GTA AGA CTC TCC TAT CTG TCT CTG TGC TGC TTT TCC GCT 464
Ala Glu Ile Val Arg Leu Ser Tyr Leu Ser Leu Cys Cys Phe Ser Ala
5 10 15

TCA AGC CCC ACA AGC ATG AAG GGG TTT CTG CTC ATC TTC AGC CTG CTT 512
Ser Ser Pro Thr Ser Met Lys Gly Phe Leu Leu Ile Phe Ser Leu Leu
20 25 30 35

GTG CAT TGT CCC CTA ATT CAT GTT GGG ACC ATT AGC TTC TAT GCT GCA 560
Val His Cys Pro Leu Ile His Val Gly Thr Ile Ser Phe Tyr Ala Ala
40 45 50

AGG CCC GGG TCT GAG CCT AAC GCG ACT TAT GTT TGT GAC TAT GGA AGC 608
Arg Pro Gly Ser Glu Pro Asn Ala Thr Tyr Val Cys Asp Tyr Gly Ser
55 60 65

GAG TCA GAT TAC AAC CCC ACC ACG GTT CTG TGG TTG GCT CGA GAG ACC 656
Glu Ser Asp Tyr Asn Pro Thr Thr Val Leu Trp Leu Ala Arg Glu Thr
70 75 80

GAT GGC TCC TGG ATC TCT GTT CTT TTC CGT CAC AAC GGC TCC TCA ACT 704
Asp Gly Ser Trp Ile Ser Val Leu Phe Arg His Asn Gly Ser Ser Thr
85 90 95

GCA GCC CCC GGG GTC GTC GCG CAC TTT ACT GAC CAC AAC AGC AGC ATT 752
Ala Ala Pro Gly Val Val Ala His Phe Thr Asp His Asn Ser Ser Ile
100 105 110 115

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GTG GTG CCC CAG TAT TAC CTC CTC AAC AAC TCA CTC TCT AAG CTC TGC      800
Val Val Pro Gln Tyr Tyr Leu Leu Asn Asn Ser Leu Ser Lys Leu Cys
                120                 125                 130

TGC TCA TAC CGG CAC AAC GAG CGT TCT CAG TTT ACC TGC AAA CAA GCT      848
Cys Ser Tyr Arg His Asn Glu Arg Ser Gln Phe Thr Cys Lys Gln Ala
            135                 140                 145

GAC GTC CCT ACC TGT CAC GAG CCC GGC AAG CCG CTC ACC CTC CGC GTC      896
Asp Val Pro Thr Cys His Glu Pro Gly Lys Pro Leu Thr Leu Arg Val
        150                 155                 160

TCC CCC GCG CTG GGA ACT GCC CAC CAA GCA GTC ACT TGG TTT TTT CAA      944
Ser Pro Ala Leu Gly Thr Ala His Gln Ala Val Thr Trp Phe Phe Gln
    165                 170                 175

AAT GTA CCC ATA GCT ACT GTT TAC CGA CCT TGG GGC AAT GTA ACT TGG      992
Asn Val Pro Ile Ala Thr Val Tyr Arg Pro Trp Gly Asn Val Thr Trp
180                 185                 190                 195

TTT TGT CCT CCC TTC ATG TGT ACC TTT AAT GTC AGC CTG AAC TCC CTA     1040
Phe Cys Pro Pro Phe Met Cys Thr Phe Asn Val Ser Leu Asn Ser Leu
                200                 205                 210

CTT ATT TAC AAC TTT TCT GAC AAA ACC GGG GGG CAA TAC ACA GCT CTC     1088
Leu Ile Tyr Asn Phe Ser Asp Lys Thr Gly Gly Gln Tyr Thr Ala Leu
            215                 220                 225

ATG CAC TCC GGA CCT GCT TCC CTC TTT CAG CTC TTT AAG CCA ACG ACT     1136
Met His Ser Gly Pro Ala Ser Leu Phe Gln Leu Phe Lys Pro Thr Thr
        230                 235                 240

TGT GTC ACC AAG GTG GAG GAC CCG CCG TAT GCC AAC GAC CCG GCC TCG     1184
Cys Val Thr Lys Val Glu Asp Pro Pro Tyr Ala Asn Asp Pro Ala Ser
    245                 250                 255

CCT GTG TGG CGC CCA CTG CTT TTT GCC TTC GTC CTC TGC ACC GGC TGC     1232
Pro Val Trp Arg Pro Leu Leu Phe Ala Phe Val Leu Cys Thr Gly Cys
260                 265                 270                 275

GCG GTG TTG TTA ACC GCC TTC GGT CCA TCG ATT CTA TCC GGT ACC CGA     1280
Ala Val Leu Leu Thr Ala Phe Gly Pro Ser Ile Leu Ser Gly Thr Arg
                280                 285                 290

AAG CTT ATC TCA GCC CGC TTT TGG AGT CCC GAG CCC TAT ACC ACC CTC     1328
Lys Leu Ile Ser Ala Arg Phe Trp Ser Pro Glu Pro Tyr Thr Thr Leu
            295                 300                 305

CAC TAACAGTCCC CCCATGGAGC CAGACGGAGT TCATGCCGAG CAGCAGTTTA          1381
His

TCCTCAATCA GATTTCCTGC GCCAACACTG CCCTCCAGCG TCAAAGGGAG GAACTAGCTT   1441

CCCTTGTCAT GTTGCATGCC TGTAAGCGTG GCCTCTTTTG TCCAGTCAAA ACTTACAAGC   1501

TCAGCCTCAA CGCCTCGGCC AGCGAGCACA GCCTGCACTT TGAAAAAAGT CCCTCCCGAT   1561

TCACCCTGGT CAACACTCAC GCCGGAGCTT CTGTGCGAGT GGCCCTACAC CACCAGGGAG   1621

CTTCCGGCAG CATCCGCTGT TCCTGTTCCC ACGCCGAGTG CCTCCCCGTC CTCCTCAAGA   1681

CCCTCTGTGC CTTTAACTTT TTAGATTAGC TGAAAGCAAA TATAAAATGG TGTGCTTACC   1741

GTAATTCTGT TTTGACTTGT GTGCTTGATT TCTCCCCCTG CGCCGTAATC CAGTGCCCCT   1801

CTTCAAAACT CTCGTACCCT ATGCGATTCG CATAGGCATA TTTTCTAAAA GCTCTGAAGT   1861

CAACATCACT CTCAAACACT TCTCCGTTGT AGGTTACTTT CATCTACAGA TAAAGTCATC   1921

CACCGGTTAA CATCATGAAG AGAAGTGTGC CCCAGGACTT TAATCTTGTG TATCCGTACA   1981

AGGCTAAGAG GCCCAACATC ATGCCGCCCT TTTTTGACCG CAATGGCTTT GTTGAAAACC   2041

AAGAAGCCAC GCTAGCCATG CTTGTGGAAA AGCCGCTCAC GTTCGACAAG GAAGGTGCGC   2101

TGACCCTGGG CGTCGGACGC GGCATCCGCA TTAACCCCGC GGGGCTTCTG GAGACAAACG   2161
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ACCTCGCGTC CGCTGTCTTC CCACCGCTGG CCTCCGATGA GGCCGGCAAC GTCACGCTCA 2221

ACATGTCTGA CGGGCTATAT ACTAAGGACA ACAAGCTAGC TGTCAAAGTA GGTCCCGGGC 2281

TGTCCCTCGA CTCCAATAAT GCTCTCCAGG TCCACACAGG CGACGGGCTC ACGGTAACCG 2341

ATGACAAGGT GTCTCTAAAT ACCCAAGCTC CCCTCTCGAC CACCAGCGCG GGCCTCTCCC 2401

TACTTCTGGG TCCCAGCCTC CACTTAGGTG AGGAGGAACG ACTAACAGTA AACACCGGAG 2461

CGGGCCTCCA AATTAGCAAT AACGCTCTGG CCGTAAAAGT AGGTTCAGGT ATCACCGTAG 2521

ATGCTCAAAA CCAGCTCGCT GCATCCCTGG GGGACGGTCT AGAAAGCAGA GATAATAAAA 2581

CTGTCGTTAA GGCTGGGCCC GGACTTACAA TAACTAATCA AGCTCTTACT GTTGCTACCG 2641

GGAACGGCCT TCAGGTCAAC CCGGAAGGGC AACTGCAGCT AAACATTACT GCCGGTCAGG 2701

GCCTCAACTT TGCAAACAAC AGCCTCGCCG TGGAGCTGGG CTCGGGCCTG CATTTTCCCC 2761

CTGGCCAAAA CCAAGTAAGC CTTTATCCCG GAGATGGAAT AGACATCCGA GATAATAGGG 2821

TGACTGTGCC CGCTGGGCCA GGCCTGAGAA TGCTCAACCA CCAACTTGCC GTAGCTTCCG 2881

GAGACGGTTT AGAAGTCCAC AGCGACACCC TCCGGTTAAA GCTCTCCCAC GGCCTGACAT 2941

TTGAAAATGG CGCCGTACGA GCAAAACTAG GACCAGGACT TGGCACAGAC GACTCTGGTC 3001

GGTCCGTGGT TCGCACAGGT CGAGGACTTA GAGTTGCAAA CGGCCAAGTC CAGATCTTCA 3061

GCGGAAGAGG CACCGCCATC GGCACTGATA GCAGCCTCAC TCTCAACATC CGGGCGCCCC 3121

TACAATTTTC TGGACCCGCC TTGACTGCTA GTTTGCAAGG CAGTGGTCCG ATTACTTACA 3181

ACAGCAACAA TGGCACTTTC GGTCTCTCTA TAGGCCCCGG AATGTGGGTA GACCAAAACA 3241

GACTTCAGGT AAACCCAGGC GCTGGTTTAG TCTTCCAAGG AAACAACCTT GTCCCAAACC 3301

TTGCGGATCC GCTGGCTATT TCCGACAGCA AAATTAGTCT CAGTCTCGGT CCCGGCCTGA 3361

CCCAAGCTTC CAACGCCCTG ACTTTAAGTT TAGGAAACGG GCTTGAATTC TCCAATCAAG 3421

CCGTTGCTAT AAAAGCGGGC CGGGGCTTAC GCTTTGAGTC TTCCTCACAA GCTTTAGAGA 3481

GCAGCCTCAC AGTCGGAAAT GGCTTAACGC TTACCGATAC TGTGATCCGC CCCAACCTAG 3541

GGGACGGCCT AGAGGTCAGA GACAATAAAA TCATTGTTAA GCTGGGCGCG AATCTTCGTT 3601

TTGAAAACGG AGCCGTAACC GCCGGCACCG TTAACCCTTC TGCGCCCGAG GCACCACCAA 3661

CTCTCACTGC AGAACCACCC CTCCGAGCCT CCAACTCCCA TCTTCAACTG TCCCTATCGG 3721

AGGGCTTGGT TGTGCATAAC AACGCCCTTG CTCTCCAACT GGGAGACGGC ATGGAAGTAA 3781

ATCAGCACGG ACTTACTTTA AGAGTAGGCT CGGGTTTGCA AATGCGTGAC GGCATTTTAA 3841

CAGTTACACC CAGCGGCACT CCTATTGAGC CCAGACTGAC TGCCCCACTG ACTCAGACAG 3901

AGAATGGAAT CGGGCTCGCT CTCGGCGCCG GCTTGGAATT AGACGAGAGC GCGCTCCAAG 3961

TAAAAGTTGG GCCCGGCATG CGCCTGAACC CTGTAGAAAA GTATGTAACC CTGCTCCTGG 4021

GTCCTGGCCT TAGTTTTGGG CAGCCGGCCA ACAGGACAAA TTATGATGTG CGCGTTTCTG 4081

TGGAGCCCCC CATGGTTTTC GGACAGCGTG GTCAGCTCAC ATTTTTAGTG GGTCACGGAC 4141

TACACATTCA AAATTCCAAA CTTCAGCTCA ATTTGGGACA AGGCCTCAGA ACTGACCCCG 4201

TCACCAACCA GCTGGAAGTG CCCCTCGGTC AAGGTTTGGA AATTGCAGAC GAATCCCAGG 4261

TTAGGGTTAA ATTGGGCGAT GGCCTGCAGT TTGATTCACA AGCTCGCATC ACTACCGCTC 4321

CTAACATGGT CACTGAAACT CTGTGGACCG GAACAGGCAG TAATGCTAAT GTTACATGGC 4381

GGGGCTACAC TGCCCCCGGC AGCAAACTCT TTTTGAGTCT CACTCGGTTC AGCACTGGTC 4441

TAGTTTTAGG AAACATGACT ATTGACAGCA ATGCATCCTT TGGGCAATAC ATTAACGCGG 4501

GACACGAACA GATCGAATGC TTTATATTGT TGGACAATCA GGGTAACCTA AAAGAAGGAT 4561

CTAACTTGCA AGGCACTTGG GAAGTGAAGA ACAACCCCTC TGCTTCCAAA GCTGCTTTTT 4621

TGCCTTCCAC CGCCCTATAC CCCATCCTCA ACGAAAGCCG AGGGAGTCTT CCTGGAAAAA 4681

ATCTTGTGGG CATGCAAGCC ATACTGGGAG GCGGGGGCAC TTGCACTGTG ATAGCCACCC 4741

TCAATGGCAG ACGCAGCAAC AACTATCCCG CGGGCCAGTC CATAATTTTC GTGTGGCAAG 4801

AATTCAACAC CATAGCCCGC CAACCTCTGA ACCACTCTAC ACTTACTTTT TCTTACTGGA 4861

CTTAAATAAG TTGGAAATAA AGAGTTAAAC TGAATGTTTA AGTGCAACAG ACTTTTATTG 4921

GTTTTGGCTC ACAACAAATT ACAACAGCAT AGACAAGTCA TACCGGTCAA ACAACACAGG 4981

CTCTCGAAAA CGGGCTAACC GCTCCAAGAA TCTGTCACGC AGACGAGCAA GTCCTAAATG 5041

TTTTTTCACT CTCTTCGGGG CCAAGTTCAG CATGTATCGG ATTTTCTGCT TACACCTTT 5100

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 308 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Ala Val Ile Ala Glu Ile Val Arg Leu Ser Tyr Leu Ser Leu Cys Cys
1 5 10 15

Phe Ser Ala Ser Ser Pro Thr Ser Met Lys Gly Phe Leu Leu Ile Phe
20 25 30

Ser Leu Leu Val His Cys Pro Leu Ile His Val Gly Thr Ile Ser Phe
35 40 45

Tyr Ala Ala Arg Pro Gly Ser Glu Pro Asn Ala Thr Tyr Val Cys Asp
50 55 60

Tyr Gly Ser Glu Ser Asp Tyr Asn Pro Thr Thr Val Leu Trp Leu Ala
65 70 75 80

Arg Glu Thr Asp Gly Ser Trp Ile Ser Val Leu Phe Arg His Asn Gly
85 90 95

Ser Ser Thr Ala Ala Pro Gly Val Val Ala His Phe Thr Asp His Asn
100 105 110

Ser Ser Ile Val Val Pro Gln Tyr Tyr Leu Leu Asn Asn Ser Leu Ser
115 120 125

Lys Leu Cys Cys Ser Tyr Arg His Asn Glu Arg Ser Gln Phe Thr Cys
130 135 140

Lys Gln Ala Asp Val Pro Thr Cys His Glu Pro Gly Lys Pro Leu Thr
145 150 155 160

Leu Arg Val Ser Pro Ala Leu Gly Thr Ala His Gln Ala Val Thr Trp
165 170 175

Phe Phe Gln Asn Val Pro Ile Ala Thr Val Tyr Arg Pro Trp Gly Asn
180 185 190

Val Thr Trp Phe Cys Pro Pro Phe Met Cys Thr Phe Asn Val Ser Leu
195 200 205

Asn Ser Leu Leu Ile Tyr Asn Phe Ser Asp Lys Thr Gly Gly Gln Tyr
210 215 220

Thr Ala Leu Met His Ser Gly Pro Ala Ser Leu Phe Gln Leu Phe Lys
225 230 235 240

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Pro Thr Thr Cys Val Thr Lys Val Glu Asp Pro Pro Tyr Ala Asn Asp
                245                 250                 255

Pro Ala Ser Pro Val Trp Arg Pro Leu Leu Phe Ala Phe Val Leu Cys
            260                 265                 270

Thr Gly Cys Ala Val Leu Leu Thr Ala Phe Gly Pro Ser Ile Leu Ser
        275                 280                 285

Gly Thr Arg Lys Leu Ile Ser Ala Arg Phe Trp Ser Pro Glu Pro Tyr
    290                 295                 300

Thr Thr Leu His
305
```

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5100 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 529..954

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

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CCTCATCAAA CAACCCGTGG TGGGCACCAC CCACGTGGAA ATGCCTCGCA ACGAAGTCCT      60

AGAACAACAT CTGACCTCAC ATGGCGCTCA AATCGCGGGC GGAGGCGCTG CGGGCGATTA     120

CTTTAAAAGC CCCACTTCAG CTCGAACCCT TATCCCGCTC ACCGCCTCCT GCTTAAGACC     180

AGATGGAGTC TTTCAACTAG GAGGAGGCTC GCGTTCATCT TTCAACCCCC TGCAAACAGA     240

TTTTGCCTTC CACGCCCTGC CCTCCAGACC GCGCCACGGG GGCATAGGAT CCAGGCAGTT     300

TGTAGAGGAA TTTGTGCCCG CCGTCTACCT CAACCCCTAC TCGGGACCGC CGGACTCTTA     360

TCCGGACCAG TTTATACGCC ACTACAACGT GTACAGCAAC TCTGTGAGCG GTTATAGCTG     420

AGATTGTAAG ACTCTCCTAT CTGTCTCTGT GCTGCTTTTC CGCTTCAAGC CCCACAAGCA     480

TGAAGGGGTT TCTGCTCATC TTCAGCCTGC TTGTGCATTG TCCCCTAA TTC ATG TTG      537
                                                    Phe Met Leu
                                                      1

GGA CCA TTA GCT TCT ATG CTG CAA GGC CCG GGT CTG AGC CTA ACG CGA       585
Gly Pro Leu Ala Ser Met Leu Gln Gly Pro Gly Leu Ser Leu Thr Arg
  5                  10                  15

CTT ATG TTT GTG ACT ATG GAA GCG AGT CAG ATT ACA ACC CCA CCA CGG       633
Leu Met Phe Val Thr Met Glu Ala Ser Gln Ile Thr Thr Pro Pro Arg
 20                  25                  30                  35

TTC TGT GGT TGG CTC GAG AGA CCG ATG GCT CCT GGA TCT CTG TTC TTT       681
Phe Cys Gly Trp Leu Glu Arg Pro Met Ala Pro Gly Ser Leu Phe Phe
                 40                  45                  50

TCC GTC ACA ACG GCT CCT CAA CTG CAG CCC CCG GGG TCG TCG CGC ACT       729
Ser Val Thr Thr Ala Pro Gln Leu Gln Pro Pro Gly Ser Ser Arg Thr
             55                  60                  65

TTA CTG ACC ACA ACA GCA GCA TTG TGG TGC CCC AGT ATT ACC TCC TCA       777
Leu Leu Thr Thr Thr Ala Ala Leu Trp Cys Pro Ser Ile Thr Ser Ser
         70                  75                  80

ACA ACT CAC TCT CTA AGC TCT GCT GCT CAT ACC GGC ACA ACG AGC GTT       825
Thr Thr His Ser Leu Ser Ser Ala Ala His Thr Gly Thr Thr Ser Val
     85                  90                  95
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CTC AGT TTA CCT GCA AAC AAG CTG ACG TCC CTA CCT GTC ACG AGC CCG 873
Leu Ser Leu Pro Ala Asn Lys Leu Thr Ser Leu Pro Val Thr Ser Pro
100 105 110 115

GCA AGC CGC TCA CCC TCC GCG TCT CCC CCG CGC TGG GAA CTG CCC ACC 921
Ala Ser Arg Ser Pro Ser Ala Ser Pro Pro Arg Trp Glu Leu Pro Thr
120 125 130

AAG CAG TCA CTT GGT TTT TTC AAA ATG TAC CCA TAGCTACTGT TTACCGACCT 974
Lys Gln Ser Leu Gly Phe Phe Lys Met Tyr Pro
135 140

TGGGGCAATG TAACTTGGTT TTGTCCTCCC TTCATGTGTA CCTTTAATGT CAGCCTGAAC 1034

TCCCTACTTA TTTACAACTT TTCTGACAAA ACCGGGGGGC AATACACAGC TCTCATGCAC 1094

TCCGGACCTG CTTCCCTCTT TCAGCTCTTT AAGCCAACGA CTTGTGTCAC CAAGGTGGAG 1154

GACCCGCCGT ATGCCAACGA CCCGGCCTCG CCTGTGTGGC GCCCACTGCT TTTTGCCTTC 1214

GTCCTCTGCA CCGGCTGCGC GGTGTTGTTA ACCGCCTTCG GTCCATCGAT TCTATCCGGT 1274

ACCCGAAAGC TTATCTCAGC CCGCTTTTGG AGTCCCGAGC CCTATACCAC CCTCCACTAA 1334

CAGTCCCCCC ATGGAGCCAG ACGGAGTTCA TGCCGAGCAG CAGTTTATCC TCAATCAGAT 1394

TTCCTGCGCC AACACTGCCC TCCAGCGTCA AAGGGAGGAA CTAGCTTCCC TTGTCATGTT 1454

GCATGCCTGT AAGCGTGGCC TCTTTTGTCC AGTCAAAACT TACAAGCTCA GCCTCAACGC 1514

CTCGGCCAGC GAGCACAGCC TGCACTTTGA AAAAAGTCCC TCCCGATTCA CCCTGGTCAA 1574

CACTCACGCC GGAGCTTCTG TGCGAGTGGC CCTACACCAC CAGGGAGCTT CCGGCAGCAT 1634

CCGCTGTTCC TGTTCCCACG CCGAGTGCCT CCCCGTCCTC CTCAAGACCC TCTGTGCCTT 1694

TAACTTTTTA GATTAGCTGA AAGCAAATAT AAAATGGTGT GCTTACCGTA ATTCTGTTTT 1754

GACTTGTGTG CTTGATTTCT CCCCCTGCGC CGTAATCCAG TGCCCCTCTT CAAAACTCTC 1814

GTACCCTATG CGATTCGCAT AGGCATATTT TCTAAAAGCT CTGAAGTCAA CATCACTCTC 1874

AAACACTTCT CCGTTGTAGG TTACTTTCAT CTACAGATAA AGTCATCCAC CGGTTAACAT 1934

CATGAAGAGA AGTGTGCCCC AGGACTTTAA TCTTGTGTAT CCGTACAAGG CTAAGAGGCC 1994

CAACATCATG CCGCCCTTTT TTGACCGCAA TGGCTTTGTT GAAAACCAAG AAGCCACGCT 2054

AGCCATGCTT GTGGAAAAGC CGCTCACGTT CGACAAGGAA GGTGCGCTGA CCCTGGGCGT 2114

CGGACGCGGC ATCCGCATTA ACCCCGCGGG GCTTCTGGAG ACAAACGACC TCGCGTCCGC 2174

TGTCTTCCCA CCGCTGGCCT CCGATGAGGC CGGCAACGTC ACGCTCAACA TGTCTGACGG 2234

GCTATATACT AAGGACAACA AGCTAGCTGT CAAAGTAGGT CCCGGGCTGT CCCTCGACTC 2294

CAATAATGCT CTCCAGGTCC ACACAGGCGA CGGGCTCACG GTAACCGATG ACAAGGTGTC 2354

TCTAAATACC CAAGCTCCCC TCTCGACCAC CAGCGCGGGC CTCTCCCTAC TTCTGGGTCC 2414

CAGCCTCCAC TTAGGTGAGG AGGAACGACT AACAGTAAAC ACCGGAGCGG GCCTCCAAAT 2474

TAGCAATAAC GCTCTGGCCG TAAAAGTAGG TTCAGGTATC ACCGTAGATG CTCAAAACCA 2534

GCTCGCTGCA TCCCTGGGGG ACGGTCTAGA AAGCAGAGAT AATAAAACTG TCGTTAAGGC 2594

TGGGCCCGGA CTTACAATAA CTAATCAAGC TCTTACTGTT GCTACCGGGA ACGGCCTTCA 2654

GGTCAACCCG GAAGGGCAAC TGCAGCTAAA CATTACTGCC GGTCAGGGCC TCAACTTTGC 2714

AAACAACAGC CTCGCCGTGG AGCTGGGCTC GGGCCTGCAT TTTCCCCCTG GCCAAAACCA 2774

AGTAAGCCTT TATCCCGGAG ATGGAATAGA CATCCGAGAT AATAGGGTGA CTGTGCCCGC 2834

TGGGCCAGGC CTGAGAATGC TCAACCACCA ACTTGCCGTA GCTTCCGGAG ACGGTTTAGA 2894

AGTCCACAGC GACACCCTCC GGTTAAAGCT CTCCCACGGC CTGACATTTG AAAATGGCGC 2954

CGTACGAGCA AAACTAGGAC CAGGACTTGG CACAGACGAC TCTGGTCGGT CCGTGGTTCG 3014

CACAGGTCGA GGACTTAGAG TTGCAAACGG CCAAGTCCAG ATCTTCAGCG GAAGAGGCAC 3074

CGCCATCGGC ACTGATAGCA GCCTCACTCT CAACATCCGG GCGCCCCTAC AATTTTCTGG 3134

ACCCGCCTTG ACTGCTAGTT TGCAAGGCAG TGGTCCGATT ACTTACAACA GCAACAATGG 3194

CACTTTCGGT CTCTCTATAG GCCCCGGAAT GTGGGTAGAC CAAAACAGAC TTCAGGTAAA 3254

CCCAGGCGCT GGTTTAGTCT TCCAAGGAAA CAACCTTGTC CCAAACCTTG CGGATCCGCT 3314

GGCTATTTCC GACAGCAAAA TTAGTCTCAG TCTCGGTCCC GGCCTGACCC AAGCTTCCAA 3374

CGCCCTGACT TTAAGTTTAG GAAACGGGCT TGAATTCTCC AATCAAGCCG TTGCTATAAA 3434

AGCGGGCCGG GGCTTACGCT TTGAGTCTTC CTCACAAGCT TTAGAGAGCA GCCTCACAGT 3494

CGGAAATGGC TTAACGCTTA CCGATACTGT GATCCGCCCC AACCTAGGGG ACGGCCTAGA 3554

GGTCAGAGAC AATAAAATCA TTGTTAAGCT GGGCGCGAAT CTTCGTTTTG AAAACGGAGC 3614

CGTAACCGCC GGCACCGTTA ACCCTTCTGC GCCCGAGGCA CCACCAACTC TCACTGCAGA 3674

ACCACCCCTC CGAGCCTCCA ACTCCCATCT TCAACTGTCC CTATCGGAGG GCTTGGTTGT 3734

GCATAACAAC GCCCTTGCTC TCCAACTGGG AGACGGCATG GAAGTAAATC AGCACGGACT 3794

TACTTTAAGA GTAGGCTCGG GTTTGCAAAT GCGTGACGGC ATTTTAACAG TTACACCCAG 3854

CGGCACTCCT ATTGAGCCCA GACTGACTGC CCCACTGACT CAGACAGAGA ATGGAATCGG 3914

GCTCGCTCTC GGCGCCGGCT TGGAATTAGA CGAGAGCGCG CTCCAAGTAA AAGTTGGGCC 3974

CGGCATGCGC CTGAACCCTG TAGAAAAGTA TGTAACCCTG CTCCTGGGTC CTGGCCTTAG 4034

TTTTGGGCAG CCGGCCAACA GGACAAATTA TGATGTGCGC GTTTCTGTGG AGCCCCCCAT 4094

GGTTTTCGGA CAGCGTGGTC AGCTCACATT TTTAGTGGGT CACGGACTAC ACATTCAAAA 4154

TTCCAAACTT CAGCTCAATT TGGGACAAGG CCTCAGAACT GACCCCGTCA CCAACCAGCT 4214

GGAAGTGCCC CTCGGTCAAG GTTTGGAAAT TGCAGACGAA TCCCAGGTTA GGGTTAAATT 4274

GGGCGATGGC CTGCAGTTTG ATTCACAAGC TCGCATCACT ACCGCTCCTA ACATGGTCAC 4334

TGAAACTCTG TGGACCGGAA CAGGCAGTAA TGCTAATGTT ACATGGCGGG GCTACACTGC 4394

CCCCGGCAGC AAACTCTTTT TGAGTCTCAC TCGGTTCAGC ACTGGTCTAG TTTTAGGAAA 4454

CATGACTATT GACAGCAATG CATCCTTTGG GCAATACATT AACGCGGGAC ACGAACAGAT 4514

CGAATGCTTT ATATTGTTGG ACAATCAGGG TAACCTAAAA GAAGGATCTA ACTTGCAAGG 4574

CACTTGGGAA GTGAAGAACA ACCCCTCTGC TTCCAAAGCT GCTTTTTTGC CTTCCACCGC 4634

CCTATACCCC ATCCTCAACG AAAGCCGAGG GAGTCTTCCT GGAAAAAATC TTGTGGGCAT 4694

GCAAGCCATA CTGGGAGGCG GGGGCACTTG CACTGTGATA GCCACCCTCA ATGGCAGACG 4754

CAGCAACAAC TATCCCGCGG GCCAGTCCAT AATTTTCGTG TGGCAAGAAT TCAACACCAT 4814

AGCCCGCCAA CCTCTGAACC ACTCTACACT TACTTTTTCT TACTGGACTT AAATAAGTTG 4874

GAAATAAAGA GTTAAACTGA ATGTTTAAGT GCAACAGACT TTTATTGGTT TTGGCTCACA 4934

ACAAATTACA ACAGCATAGA CAAGTCATAC CGGTCAAACA ACACAGGCTC TCGAAAACGG 4994

GCTAACCGCT CCAAGAATCT GTCACGCAGA CGAGCAAGTC CTAAATGTTT TTTCACTCTC 5054

TTCGGGGCCA AGTTCAGCAT GTATCGGATT TTCTGCTTAC ACCTTT 5100

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 142 amino acids

(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Phe Met Leu Gly Pro Leu Ala Ser Met Leu Gln Gly Pro Gly Leu Ser
1 5 10 15

Leu Thr Arg Leu Met Phe Val Thr Met Glu Ala Ser Gln Ile Thr Thr
20 25 30

Pro Pro Arg Phe Cys Gly Trp Leu Glu Arg Pro Met Ala Pro Gly Ser
35 40 45

Leu Phe Phe Ser Val Thr Thr Ala Pro Gln Leu Gln Pro Pro Gly Ser
50 55 60

Ser Arg Thr Leu Leu Thr Thr Thr Ala Ala Leu Trp Cys Pro Ser Ile
65 70 75 80

Thr Ser Ser Thr Thr His Ser Leu Ser Ser Ala Ala His Thr Gly Thr
85 90 95

Thr Ser Val Leu Ser Leu Pro Ala Asn Lys Leu Thr Ser Leu Pro Val
100 105 110

Thr Ser Pro Ala Ser Arg Ser Pro Ser Ala Ser Pro Pro Arg Trp Glu
115 120 125

Leu Pro Thr Lys Gln Ser Leu Gly Phe Phe Lys Met Tyr Pro
130 135 140

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5100 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1246..1707

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

CCTCATCAAA CAACCCGTGG TGGGCACCAC CCACGTGGAA ATGCCTCGCA ACGAAGTCCT 60

AGAACAACAT CTGACCTCAC ATGGCGCTCA AATCGCGGGC GGAGGCGCTG CGGGCGATTA 120

CTTTAAAAGC CCCACTTCAG CTCGAACCCT TATCCCGCTC ACCGCCTCCT GCTTAAGACC 180

AGATGGAGTC TTTCAACTAG GAGGAGGCTC GCGTTCATCT TTCAACCCCC TGCAAACAGA 240

TTTTGCCTTC CACGCCCTGC CCTCCAGACC GCGCCACGGG GGCATAGGAT CCAGGCAGTT 300

TGTAGAGGAA TTTGTGCCCG CCGTCTACCT CAACCCCTAC TCGGGACCGC CGGACTCTTA 360

TCCGGACCAG TTTATACGCC ACTACAACGT GTACAGCAAC TCTGTGAGCG GTTATAGCTG 420

AGATTGTAAG ACTCTCCTAT CTGTCTCTGT GCTGCTTTTC CGCTTCAAGC CCCACAAGCA 480

TGAAGGGGTT TCTGCTCATC TTCAGCCTGC TTGTGCATTG TCCCCTAATT CATGTTGGGA 540

CCATTAGCTT CTATGCTGCA AGGCCCGGGT CTGAGCCTAA CGCGACTTAT GTTTGTGACT 600

ATGGAAGCGA GTCAGATTAC AACCCCACCA CGGTTCTGTG GTTGGCTCGA GAGACCGATG 660

GCTCCTGGAT CTCTGTTCTT TTCCGTCACA ACGGCTCCTC AACTGCAGCC CCCGGGGTCG 720

TCGCGCACTT TACTGACCAC AACAGCAGCA TTGTGGTGCC CCAGTATTAC CTCCTCAACA 780

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ACTCACTCTC TAAGCTCTGC TGCTCATACC GGCACAACGA GCGTTCTCAG TTTACCTGCA    840

AACAAGCTGA CGTCCCTACC TGTCACGAGC CCGGCAAGCC GCTCACCCTC CGCGTCTCCC    900

CCGCGCTGGG AACTGCCCAC CAAGCAGTCA CTTGGTTTTT TCAAAATGTA CCCATAGCTA    960

CTGTTTACCG ACCTTGGGGC AATGTAACTT GGTTTTGTCC TCCCTTCATG TGTACCTTTA   1020

ATGTCAGCCT GAACTCCCTA CTTATTTACA ACTTTTCTGA CAAAACCGGG GGGCAATACA   1080

CAGCTCTCAT GCACTCCGGA CCTGCTTCCC TCTTTCAGCT CTTTAAGCCA ACGACTTGTG   1140

TCACCAAGGT GGAGGACCCG CCGTATGCCA ACGACCCGGC CTCGCCTGTG TGGCGCCCAC   1200

TGCTTTTTGC CTTCGTCCTC TGCACCGGCT GCGCGGTGTT GTTAA CCG CCT TCG       1254
                                                  Pro Pro Ser
                                                    1

GTC CAT CGA TTC TAT CCG GTA CCC GAA AGC TTA TCT CAG CCC GCT TTT      1302
Val His Arg Phe Tyr Pro Val Pro Glu Ser Leu Ser Gln Pro Ala Phe
  5                  10                  15

GGA GTC CCG AGC CCT ATA CCA CCC TCC ACT AAC AGT CCC CCC ATG GAG      1350
Gly Val Pro Ser Pro Ile Pro Pro Ser Thr Asn Ser Pro Pro Met Glu
 20                  25                  30                  35

CCA GAC GGA GTT CAT GCC GAG CAG CAG TTT ATC CTC AAT CAG ATT TCC      1398
Pro Asp Gly Val His Ala Glu Gln Gln Phe Ile Leu Asn Gln Ile Ser
              40                  45                  50

TGC GCC AAC ACT GCC CTC CAG CGT CAA AGG GAG GAA CTA GCT TCC CTT      1446
Cys Ala Asn Thr Ala Leu Gln Arg Gln Arg Glu Glu Leu Ala Ser Leu
          55                  60                  65

GTC ATG TTG CAT GCC TGT AAG CGT GGC CTC TTT TGT CCA GTC AAA ACT      1494
Val Met Leu His Ala Cys Lys Arg Gly Leu Phe Cys Pro Val Lys Thr
      70                  75                  80

TAC AAG CTC AGC CTC AAC GCC TCG GCC AGC GAG CAC AGC CTG CAC TTT      1542
Tyr Lys Leu Ser Leu Asn Ala Ser Ala Ser Glu His Ser Leu His Phe
  85                  90                  95

GAA AAA AGT CCC TCC CGA TTC ACC CTG GTC AAC ACT CAC GCC GGA GCT      1590
Glu Lys Ser Pro Ser Arg Phe Thr Leu Val Asn Thr His Ala Gly Ala
100                 105                 110                 115

TCT GTG CGA GTG GCC CTA CAC CAC CAG GGA GCT TCC GGC AGC ATC CGC      1638
Ser Val Arg Val Ala Leu His His Gln Gly Ala Ser Gly Ser Ile Arg
              120                 125                 130

TGT TCC TGT TCC CAC GCC GAG TGC CTC CCC GTC CTC CTC AAG ACC CTC      1686
Cys Ser Cys Ser His Ala Glu Cys Leu Pro Val Leu Leu Lys Thr Leu
          135                 140                 145

TGT GCC TTT AAC TTT TTA GAT TAGCTGAAAG CAAATATAAA ATGGTGTGCT         1737
Cys Ala Phe Asn Phe Leu Asp
      150

TACCGTAATT CTGTTTTGAC TTGTGTGCTT GATTTCTCCC CCTGCGCCGT AATCCAGTGC   1797

CCCTCTTCAA AACTCTCGTA CCCTATGCGA TTCGCATAGG CATATTTTCT AAAAGCTCTG   1857

AAGTCAACAT CACTCTCAAA CACTTCTCCG TTGTAGGTTA CTTTCATCTA CAGATAAAGT   1917

CATCCACCGG TTAACATCAT GAAGAGAAGT GTGCCCCAGG ACTTTAATCT TGTGTATCCG   1977

TACAAGGCTA AGAGGCCCAA CATCATGCCG CCCTTTTTTG ACCGCAATGG CTTTGTTGAA   2037

AACCAAGAAG CCACGCTAGC CATGCTTGTG GAAAAGCCGC TCACGTTCGA CAAGGAAGGT   2097

GCGCTGACCC TGGGCGTCGG ACGCGGCATC CGCATTAACC CCGCGGGGCT TCTGGAGACA   2157

AACGACCTCG CGTCCGCTGT CTTCCCACCG CTGGCCTCCG ATGAGGCCGG CAACGTCACG   2217

CTCAACATGT CTGACGGGCT ATATACTAAG GACAACAAGC TAGCTGTCAA AGTAGGTCCC   2277

GGGCTGTCCC TCGACTCCAA TAATGCTCTC CAGGTCCACA CAGGCGACGG GCTCACGGTA   2337
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ACCGATGACA AGGTGTCTCT AAATACCCAA GCTCCCCTCT CGACCACCAG CGCGGGCCTC 2397

TCCCTACTTC TGGGTCCCAG CCTCCACTTA GGTGAGGAGG AACGACTAAC AGTAAACACC 2457

GGAGCGGGCC TCCAAATTAG CAATAACGCT CTGGCCGTAA AAGTAGGTTC AGGTATCACC 2517

GTAGATGCTC AAAACCAGCT CGCTGCATCC CTGGGGGACG GTCTAGAAAG CAGAGATAAT 2577

AAAACTGTCG TTAAGGCTGG GCCCGGACTT ACAATAACTA ATCAAGCTCT TACTGTTGCT 2637

ACCGGGAACG GCCTTCAGGT CAACCCGGAA GGGCAACTGC AGCTAAACAT TACTGCCGGT 2697

CAGGGCCTCA ACTTTGCAAA CAACAGCCTC GCCGTGGAGC TGGGCTCGGG CCTGCATTTT 2757

CCCCCTGGCC AAAACCAAGT AAGCCTTTAT CCCGGAGATG GAATAGACAT CCGAGATAAT 2817

AGGGTGACTG TGCCCGCTGG GCCAGGCCTG AGAATGCTCA ACCACCAACT TGCCGTAGCT 2877

TCCGGAGACG GTTTAGAAGT CCACAGCGAC ACCCTCCGGT TAAAGCTCTC CCACGGCCTG 2937

ACATTTGAAA ATGGCGCCGT ACGAGCAAAA CTAGGACCAG GACTTGGCAC AGACGACTCT 2997

GGTCGGTCCG TGGTTCGCAC AGGTCGAGGA CTTAGAGTTG CAAACGGCCA AGTCCAGATC 3057

TTCAGCGGAA GAGGCACCGC CATCGGCACT GATAGCAGCC TCACTCTCAA CATCCGGGCG 3117

CCCCTACAAT TTTCTGGACC CGCCTTGACT GCTAGTTTGC AAGGCAGTGG TCCGATTACT 3177

TACAACAGCA ACAATGGCAC TTTCGGTCTC TCTATAGGCC CCGGAATGTG GGTAGACCAA 3237

AACAGACTTC AGGTAAACCC AGGCGCTGGT TTAGTCTTCC AAGGAAACAA CCTTGTCCCA 3297

AACCTTGCGG ATCCGCTGGC TATTTCCGAC AGCAAAATTA GTCTCAGTCT CGGTCCCGGC 3357

CTGACCCAAG CTTCCAACGC CCTGACTTTA AGTTTAGGAA ACGGGCTTGA ATTCTCCAAT 3417

CAAGCCGTTG CTATAAAAGC GGGCCGGGGC TTACGCTTTG AGTCTTCCTC ACAAGCTTTA 3477

GAGAGCAGCC TCACAGTCGG AAATGGCTTA ACGCTTACCG ATACTGTGAT CCGCCCCAAC 3537

CTAGGGGACG GCCTAGAGGT CAGAGACAAT AAAATCATTG TTAAGCTGGG CGCGAATCTT 3597

CGTTTTGAAA ACGGAGCCGT AACCGCCGGC ACCGTTAACC CTTCTGCGCC CGAGGCACCA 3657

CCAACTCTCA CTGCAGAACC ACCCCTCCGA GCCTCCAACT CCCATCTTCA ACTGTCCCTA 3717

TCGGAGGGCT TGGTTGTGCA TAACAACGCC CTTGCTCTCC AACTGGGAGA CGGCATGGAA 3777

GTAAATCAGC ACGGACTTAC TTTAAGAGTA GGCTCGGGTT TGCAAATGCG TGACGGCATT 3837

TTAACAGTTA CACCCAGCGG CACTCCTATT GAGCCCAGAC TGACTGCCCC ACTGACTCAG 3897

ACAGAGAATG GAATCGGGCT CGCTCTCGGC GCCGGCTTGG AATTAGACGA GAGCGCGCTC 3957

CAAGTAAAAG TTGGGCCCGG CATGCGCCTG AACCCTGTAG AAAAGTATGT AACCCTGCTC 4017

CTGGGTCCTG GCCTTAGTTT TGGGCAGCCG GCCAACAGGA CAAATTATGA TGTGCGCGTT 4077

TCTGTGGAGC CCCCCATGGT TTTCGGACAG CGTGGTCAGC TCACATTTTT AGTGGGTCAC 4137

GGACTACACA TTCAAAATTC CAAACTTCAG CTCAATTTGG GACAAGGCCT CAGAACTGAC 4197

CCCGTCACCA ACCAGCTGGA AGTGCCCCTC GGTCAAGGTT TGGAAATTGC AGACGAATCC 4257

CAGGTTAGGG TTAAATTGGG CGATGGCCTG CAGTTTGATT CACAAGCTCG CATCACTACC 4317

GCTCCTAACA TGGTCACTGA AACTCTGTGG ACCGGAACAG GCAGTAATGC TAATGTTACA 4377

TGGCGGGGCT ACACTGCCCC CGGCAGCAAA CTCTTTTTGA GTCTCACTCG GTTCAGCACT 4437

GGTCTAGTTT TAGGAAACAT GACTATTGAC AGCAATGCAT CCTTTGGGCA ATACATTAAC 4497

GCGGGACACG AACAGATCGA ATGCTTTATA TTGTTGGACA ATCAGGGTAA CCTAAAAGAA 4557

GGATCTAACT TGCAAGGCAC TTGGGAAGTG AAGAACAACC CCTCTGCTTC CAAAGCTGCT 4617

TTTTTGCCTT CCACCGCCCT ATACCCCATC CTCAACGAAA GCCGAGGGAG TCTTCCTGGA 4677

AAAAATCTTG TGGGCATGCA AGCCATACTG GGAGGCGGGG GCACTTGCAC TGTGATAGCC 4737

ACCCTCAATG GCAGACGCAG CAACAACTAT CCCGCGGGCC AGTCCATAAT TTTCGTGTGG 4797

CAAGAATTCA ACACCATAGC CCGCCAACCT CTGAACCACT CTACACTTAC TTTTTCTTAC 4857

TGGACTTAAA TAAGTTGGAA ATAAAGAGTT AAACTGAATG TTTAAGTGCA ACAGACTTTT 4917

ATTGGTTTTG GCTCACAACA AATTACAACA GCATAGACAA GTCATACCGG TCAAACAACA 4977

CAGGCTCTCG AAAACGGGCT AACCGCTCCA AGAATCTGTC ACGCAGACGA GCAAGTCCTA 5037

AATGTTTTTT CACTCTCTTC GGGGCCAAGT TCAGCATGTA TCGGATTTTC TGCTTACACC 5097

TTT 5100

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 154 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Pro Pro Ser Val His Arg Phe Tyr Pro Val Pro Glu Ser Leu Ser Gln
1 5 10 15

Pro Ala Phe Gly Val Pro Ser Pro Ile Pro Pro Ser Thr Asn Ser Pro
20 25 30

Pro Met Glu Pro Asp Gly Val His Ala Glu Gln Gln Phe Ile Leu Asn
35 40 45

Gln Ile Ser Cys Ala Asn Thr Ala Leu Gln Arg Gln Arg Glu Glu Leu
50 55 60

Ala Ser Leu Val Met Leu His Ala Cys Lys Arg Gly Leu Phe Cys Pro
65 70 75 80

Val Lys Thr Tyr Lys Leu Ser Leu Asn Ala Ser Ala Ser Glu His Ser
85 90 95

Leu His Phe Glu Lys Ser Pro Ser Arg Phe Thr Leu Val Asn Thr His
100 105 110

Ala Gly Ala Ser Val Arg Val Ala Leu His His Gln Gly Ala Ser Gly
115 120 125

Ser Ile Arg Cys Ser Cys Ser His Ala Glu Cys Leu Pro Val Leu Leu
130 135 140

Lys Thr Leu Cys Ala Phe Asn Phe Leu Asp
145 150

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5100 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1439..1702

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

CCTCATCAAA CAACCCGTGG TGGGCACCAC CCACGTGGAA ATGCCTCGCA ACGAAGTCCT 60

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AGAACAACAT CTGACCTCAC ATGGCGCTCA AATCGCGGGC GGAGGCGCTG CGGGCGATTA    120

CTTTAAAAGC CCCACTTCAG CTCGAACCCT TATCCCGCTC ACCGCCTCCT GCTTAAGACC    180

AGATGGAGTC TTTCAACTAG GAGGAGGCTC GCGTTCATCT TTCAACCCCC TGCAAACAGA    240

TTTTGCCTTC CACGCCCTGC CCTCCAGACC GCGCCACGGG GGCATAGGAT CCAGGCAGTT    300

TGTAGAGGAA TTTGTGCCCG CCGTCTACCT CAACCCCTAC TCGGGACCGC CGGACTCTTA    360

TCCGGACCAG TTTATACGCC ACTACAACGT GTACAGCAAC TCTGTGAGCG GTTATAGCTG    420

AGATTGTAAG ACTCTCCTAT CTGTCTCTGT GCTGCTTTTC CGCTTCAAGC CCCACAAGCA    480

TGAAGGGGTT TCTGCTCATC TTCAGCCTGC TTGTGCATTG TCCCCTAATT CATGTTGGGA    540

CCATTAGCTT CTATGCTGCA AGGCCCGGGT CTGAGCCTAA CGCGACTTAT GTTTGTGACT    600

ATGGAAGCGA GTCAGATTAC AACCCCACCA CGGTTCTGTG GTTGGCTCGA GAGACCGATG    660

GCTCCTGGAT CTCTGTTCTT TTCCGTCACA ACGGCTCCTC AACTGCAGCC CCCGGGGTCG    720

TCGCGCACTT TACTGACCAC AACAGCAGCA TTGTGGTGCC CCAGTATTAC CTCCTCAACA    780

ACTCACTCTC TAAGCTCTGC TGCTCATACC GGCACAACGA GCGTTCTCAG TTTACCTGCA    840

AACAAGCTGA CGTCCCTACC TGTCACGAGC CCGGCAAGCC GCTCACCCTC CGCGTCTCCC    900

CCGCGCTGGG AACTGCCCAC CAAGCAGTCA CTTGGTTTTT TCAAAATGTA CCCATAGCTA    960

CTGTTTACCG ACCTTGGGGC AATGTAACTT GGTTTTGTCC TCCCTTCATG TGTACCTTTA   1020

ATGTCAGCCT GAACTCCCTA CTTATTTACA ACTTTTCTGA CAAAACCGGG GGGCAATACA   1080

CAGCTCTCAT GCACTCCGGA CCTGCTTCCC TCTTTCAGCT CTTTAAGCCA ACGACTTGTG   1140

TCACCAAGGT GGAGGACCCG CCGTATGCCA ACGACCCGGC CTCGCCTGTG TGGCGCCCAC   1200

TGCTTTTTGC CTTCGTCCTC TGCACCGGCT GCGCGGTGTT GTTAACCGCC TTCGGTCCAT   1260

CGATTCTATC CGGTACCCGA AAGCTTATCT CAGCCCGCTT TTGGAGTCCC GAGCCCTATA   1320

CCACCCTCCA CTAACAGTCC CCCCATGGAG CCAGACGGAG TTCATGCCGA GCAGCAGTTT   1380

ATCCTCAATC AGATTTCCTG CGCCAACACT GCCCTCCAGC GTCAAAGGGA GGAACTAG     1438

CTT CCC TTG TCA TGT TGC ATG CCT GTA AGC GTG GCC TCT TTT GTC CAG      1486
Leu Pro Leu Ser Cys Cys Met Pro Val Ser Val Ala Ser Phe Val Gln
 1               5                  10                  15

TCA AAA CTT ACA AGC TCA GCC TCA ACG CCT CGG CCA GCG AGC ACA GCC      1534
Ser Lys Leu Thr Ser Ser Ala Ser Thr Pro Arg Pro Ala Ser Thr Ala
            20                  25                  30

TGC ACT TTG AAA AAA GTC CCT CCC GAT TCA CCC TGG TCA ACA CTC ACG      1582
Cys Thr Leu Lys Lys Val Pro Pro Asp Ser Pro Trp Ser Thr Leu Thr
        35                  40                  45

CCG GAG CTT CTG TGC GAG TGG CCC TAC ACC ACC AGG GAG CTT CCG GCA      1630
Pro Glu Leu Leu Cys Glu Trp Pro Tyr Thr Thr Arg Glu Leu Pro Ala
    50                  55                  60

GCA TCC GCT GTT CCT GTT CCC ACG CCG AGT GCC TCC CCG TCC TCC TCA      1678
Ala Ser Ala Val Pro Val Pro Thr Pro Ser Ala Ser Pro Ser Ser Ser
65                  70                  75                  80

AGA CCC TCT GTG CCT TTA ACT TTT TAGATTAGCT GAAAGCAAAT ATAAAATGGT    1732
Arg Pro Ser Val Pro Leu Thr Phe
                85

GTGCTTACCG TAATTCTGTT TTGACTTGTG TGCTTGATTT CTCCCCCTGC GCCGTAATCC   1792

AGTGCCCCTC TTCAAAACTC TCGTACCCTA TGCGATTCGC ATAGGCATAT TTTCTAAAAG   1852

CTCTGAAGTC AACATCACTC TCAAACACTT CTCCGTTGTA GGTTACTTTC ATCTACAGAT   1912

AAAGTCATCC ACCGGTTAAC ATCATGAAGA GAAGTGTGCC CCAGGACTTT AATCTTGTGT   1972
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ATCCGTACAA GGCTAAGAGG CCCAACATCA TGCCGCCCTT TTTTGACCGC AATGGCTTTG 2032

TTGAAAACCA AGAAGCCACG CTAGCCATGC TTGTGGAAAA GCCGCTCACG TTCGACAAGG 2092

AAGGTGCGCT GACCCTGGGC GTCGGACGCG GCATCCGCAT TAACCCCGCG GGGCTTCTGG 2152

AGACAAACGA CCTCGCGTCC GCTGTCTTCC CACCGCTGGC CTCCGATGAG GCCGGCAACG 2212

TCACGCTCAA CATGTCTGAC GGGCTATATA CTAAGGACAA CAAGCTAGCT GTCAAAGTAG 2272

GTCCCGGGCT GTCCCTCGAC TCCAATAATG CTCTCCAGGT CCACACAGGC GACGGGCTCA 2332

CGGTAACCGA TGACAAGGTG TCTCTAAATA CCCAAGCTCC CCTCTCGACC ACCAGCGCGG 2392

GCCTCTCCCT ACTTCTGGGT CCCAGCCTCC ACTTAGGTGA GGAGGAACGA CTAACAGTAA 2452

ACACCGGAGC GGGCCTCCAA ATTAGCAATA ACGCTCTGGC CGTAAAAGTA GGTTCAGGTA 2512

TCACCGTAGA TGCTCAAAAC CAGCTCGCTG CATCCCTGGG GGACGGTCTA GAAAGCAGAG 2572

ATAATAAAAC TGTCGTTAAG GCTGGGCCCG GACTTACAAT AACTAATCAA GCTCTTACTG 2632

TTGCTACCGG GAACGGCCTT CAGGTCAACC CGGAAGGGCA ACTGCAGCTA AACATTACTG 2692

CCGGTCAGGG CCTCAACTTT GCAAACAACA GCCTCGCCGT GGAGCTGGGC TCGGGCCTGC 2752

ATTTTCCCCC TGGCCAAAAC CAAGTAAGCC TTTATCCCGG AGATGGAATA GACATCCGAG 2812

ATAATAGGGT GACTGTGCCC GCTGGGCCAG GCCTGAGAAT GCTCAACCAC CAACTTGCCG 2872

TAGCTTCCGG AGACGGTTTA GAAGTCCACA GCGACACCCT CCGGTTAAAG CTCTCCCACG 2932

GCCTGACATT TGAAAATGGC GCCGTACGAG CAAAACTAGG ACCAGGACTT GGCACAGACG 2992

ACTCTGGTCG GTCCGTGGTT CGCACAGGTC GAGGACTTAG AGTTGCAAAC GGCCAAGTCC 3052

AGATCTTCAG CGGAAGAGGC ACCGCCATCG GCACTGATAG CAGCCTCACT CTCAACATCC 3112

GGGCGCCCCT ACAATTTTCT GGACCCGCCT TGACTGCTAG TTTGCAAGGC AGTGGTCCGA 3172

TTACTTACAA CAGCAACAAT GGCACTTTCG GTCTCTCTAT AGGCCCCGGA ATGTGGGTAG 3232

ACCAAAACAG ACTTCAGGTA AACCCAGGCG CTGGTTTAGT CTTCCAAGGA AACAACCTTG 3292

TCCCAAACCT TGCGGATCCG CTGGCTATTT CCGACAGCAA AATTAGTCTC AGTCTCGGTC 3352

CCGGCCTGAC CCAAGCTTCC AACGCCCTGA CTTTAAGTTT AGGAAACGGG CTTGAATTCT 3412

CCAATCAAGC CGTTGCTATA AAAGCGGGCC GGGGCTTACG CTTTGAGTCT TCCTCACAAG 3472

CTTTAGAGAG CAGCCTCACA GTCGGAAATG GCTTAACGCT TACCGATACT GTGATCCGCC 3532

CCAACCTAGG GGACGGCCTA GAGGTCAGAG ACAATAAAAT CATTGTTAAG CTGGGCGCGA 3592

ATCTTCGTTT TGAAAACGGA GCCGTAACCG CCGGCACCGT TAACCCTTCT GCGCCCGAGG 3652

CACCACCAAC TCTCACTGCA GAACCACCCC TCCGAGCCTC CAACTCCCAT CTTCAACTGT 3712

CCCTATCGGA GGGCTTGGTT GTGCATAACA ACGCCCTTGC TCTCCAACTG GGAGACGGCA 3772

TGGAAGTAAA TCAGCACGGA CTTACTTTAA GAGTAGGCTC GGGTTTGCAA ATGCGTGACG 3832

GCATTTTAAC AGTTACACCC AGCGGCACTC CTATTGAGCC CAGACTGACT GCCCCACTGA 3892

CTCAGACAGA GAATGGAATC GGGCTCGCTC TCGGCGCCGG CTTGGAATTA GACGAGAGCG 3952

CGCTCCAAGT AAAAGTTGGG CCCGGCATGC GCCTGAACCC TGTAGAAAAG TATGTAACCC 4012

TGCTCCTGGG TCCTGGCCTT AGTTTTGGGC AGCCGGCCAA CAGGACAAAT TATGATGTGC 4072

GCGTTTCTGT GGAGCCCCCC ATGGTTTTCG GACAGCGTGG TCAGCTCACA TTTTTAGTGG 4132

GTCACGGACT ACACATTCAA AATTCCAAAC TTCAGCTCAA TTTGGGACAA GGCCTCAGAA 4192

CTGACCCCGT CACCAACCAG CTGGAAGTGC CCCTCGGTCA AGGTTTGGAA ATTGCAGACG 4252

AATCCCAGGT TAGGGTTAAA TTGGGCGATG GCCTGCAGTT TGATTCACAA GCTCGCATCA 4312

CTACCGCTCC TAACATGGTC ACTGAAACTC TGTGGACCGG AACAGGCAGT AATGCTAATG 4372

TTACATGGCG GGGCTACACT GCCCCCGGCA GCAAACTCTT TTTGAGTCTC ACTCGGTTCA 4432

GCACTGGTCT AGTTTTAGGA AACATGACTA TTGACAGCAA TGCATCCTTT GGGCAATACA 4492

TTAACGCGGG ACACGAACAG ATCGAATGCT TTATATTGTT GGACAATCAG GGTAACCTAA 4552

AAGAAGGATC TAACTTGCAA GGCACTTGGG AAGTGAAGAA CAACCCCTCT GCTTCCAAAG 4612

CTGCTTTTTT GCCTTCCACC GCCCTATACC CCATCCTCAA CGAAAGCCGA GGGAGTCTTC 4672

CTGGAAAAAA TCTTGTGGGC ATGCAAGCCA TACTGGGAGG CGGGGGCACT TGCACTGTGA 4732

TAGCCACCCT CAATGGCAGA CGCAGCAACA ACTATCCCGC GGGCCAGTCC ATAATTTTCG 4792

TGTGGCAAGA ATTCAACACC ATAGCCCGCC AACCTCTGAA CCACTCTACA CTTACTTTTT 4852

CTTACTGGAC TTAAATAAGT TGGAAATAAA GAGTTAAACT GAATGTTTAA GTGCAACAGA 4912

CTTTTATTGG TTTTGGCTCA CAACAAATTA CAACAGCATA GACAAGTCAT ACCGGTCAAA 4972

CAACACAGGC TCTCGAAAAC GGGCTAACCG CTCCAAGAAT CTGTCACGCA GACGAGCAAG 5032

TCCTAAATGT TTTTTCACTC TCTTCGGGGC CAAGTTCAGC ATGTATCGGA TTTTCTGCTT 5092

ACACCTTT 5100

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 88 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Leu Pro Leu Ser Cys Cys Met Pro Val Ser Val Ala Ser Phe Val Gln
1 5 10 15

Ser Lys Leu Thr Ser Ser Ala Ser Thr Pro Arg Pro Ala Ser Thr Ala
20 25 30

Cys Thr Leu Lys Lys Val Pro Pro Asp Ser Pro Trp Ser Thr Leu Thr
35 40 45

Pro Glu Leu Leu Cys Glu Trp Pro Tyr Thr Thr Arg Glu Leu Pro Ala
50 55 60

Ala Ser Ala Val Pro Val Pro Thr Pro Ser Ala Ser Pro Ser Ser Ser
65 70 75 80

Arg Pro Ser Val Pro Leu Thr Phe
85

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5100 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1915..4863

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

CCTCATCAAA CAACCCGTGG TGGGCACCAC CCACGTGGAA ATGCCTCGCA ACGAAGTCCT 60

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AGAACAACAT CTGACCTCAC ATGGCGCTCA AATCGCGGGC GGAGGCGCTG CGGGCGATTA   120
CTTTAAAAGC CCCACTTCAG CTCGAACCCT TATCCCGCTC ACCGCCTCCT GCTTAAGACC   180
AGATGGAGTC TTTCAACTAG GAGGAGGCTC GCGTTCATCT TTCAACCCCC TGCAAACAGA   240
TTTTGCCTTC CACGCCCTGC CCTCCAGACC GCGCCACGGG GGCATAGGAT CCAGGCAGTT   300
TGTAGAGGAA TTTGTGCCCG CCGTCTACCT CAACCCCTAC TCGGGACCGC CGGACTCTTA   360
TCCGGACCAG TTTATACGCC ACTACAACGT GTACAGCAAC TCTGTGAGCG GTTATAGCTG   420
AGATTGTAAG ACTCTCCTAT CTGTCTCTGT GCTGCTTTTC CGCTTCAAGC CCCACAAGCA   480
TGAAGGGGTT TCTGCTCATC TTCAGCCTGC TTGTGCATTG TCCCCTAATT CATGTTGGGA   540
CCATTAGCTT CTATGCTGCA AGGCCCGGGT CTGAGCCTAA CGCGACTTAT GTTTGTGACT   600
ATGGAAGCGA GTCAGATTAC AACCCCACCA CGGTTCTGTG GTTGGCTCGA GAGACCGATG   660
GCTCCTGGAT CTCTGTTCTT TTCCGTCACA ACGGCTCCTC AACTGCAGCC CCCGGGGTCG   720
TCGCGCACTT TACTGACCAC AACAGCAGCA TTGTGGTGCC CCAGTATTAC CTCCTCAACA   780
ACTCACTCTC TAAGCTCTGC TGCTCATACC GGCACAACGA GCGTTCTCAG TTTACCTGCA   840
AACAAGCTGA CGTCCCTACC TGTCACGAGC CCGGCAAGCC GCTCACCCTC CGCGTCTCCC   900
CCGCGCTGGG AACTGCCCAC CAAGCAGTCA CTTGGTTTTT TCAAAATGTA CCCATAGCTA   960
CTGTTTACCG ACCTTGGGGC AATGTAACTT GGTTTTGTCC TCCCTTCATG TGTACCTTTA  1020
ATGTCAGCCT GAACTCCCTA CTTATTTACA ACTTTTCTGA CAAAACCGGG GGGCAATACA  1080
CAGCTCTCAT GCACTCCGGA CCTGCTTCCC TCTTTCAGCT CTTTAAGCCA ACGACTTGTG  1140
TCACCAAGGT GGAGGACCCG CCGTATGCCA ACGACCCGGC CTCGCCTGTG TGGCGCCCAC  1200
TGCTTTTTGC CTTCGTCCTC TGCACCGGCT GCGCGGTGTT GTTAACCGCC TTCGGTCCAT  1260
CGATTCTATC CGGTACCCGA AAGCTTATCT CAGCCCGCTT TTGGAGTCCC GAGCCCTATA  1320
CCACCCTCCA CTAACAGTCC CCCCATGGAG CCAGACGGAG TTCATGCCGA GCAGCAGTTT  1380
ATCCTCAATC AGATTTCCTG CGCCAACACT GCCCTCCAGC GTCAAAGGGA GGAACTAGCT  1440
TCCCTTGTCA TGTTGCATGC CTGTAAGCGT GGCCTCTTTT GTCCAGTCAA AACTTACAAG  1500
CTCAGCCTCA ACGCCTCGGC CAGCGAGCAC AGCCTGCACT TTGAAAAAAG TCCCTCCCGA  1560
TTCACCCTGG TCAACACTCA CGCCGGAGCT TCTGTGCGAG TGGCCCTACA CCACCAGGGA  1620
GCTTCCGGCA GCATCCGCTG TTCCTGTTCC CACGCCGAGT GCCTCCCCGT CCTCCTCAAG  1680
ACCCTCTGTG CCTTTAACTT TTTAGATTAG CTGAAAGCAA ATATAAAATG GTGTGCTTAC  1740
CGTAATTCTG TTTTGACTTG TGTGCTTGAT TTCTCCCCCT GCGCCGTAAT CCAGTGCCCC  1800
TCTTCAAAAC TCTCGTACCC TATGCGATTC GCATAGGCAT ATTTTCTAAA AGCTCTGAAG  1860
TCAACATCAC TCTCAAACAC TTCTCCGTTG TAGGTTACTT TCATCTACAG ATAA AGT    1917
                                                            Ser
                                                             1

CAT CCA CCG GTT AAC ATC ATG AAG AGA AGT GTG CCC CAG GAC TTT AAT    1965
His Pro Pro Val Asn Ile Met Lys Arg Ser Val Pro Gln Asp Phe Asn
      5                  10                  15

CTT GTG TAT CCG TAC AAG GCT AAG AGG CCC AAC ATC ATG CCG CCC TTT    2013
Leu Val Tyr Pro Tyr Lys Ala Lys Arg Pro Asn Ile Met Pro Pro Phe
  20                  25                  30

TTT GAC CGC AAT GGC TTT GTT GAA AAC CAA GAA GCC ACG CTA GCC ATG    2061
Phe Asp Arg Asn Gly Phe Val Glu Asn Gln Glu Ala Thr Leu Ala Met
  35                  40                  45

CTT GTG GAA AAG CCG CTC ACG TTC GAC AAG GAA GGT GCG CTG ACC CTG    2109
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Leu Val Glu Lys Pro Leu Thr Phe Asp Lys Glu Gly Ala Leu Thr Leu
 50                  55                  60                  65

GGC GTC GGA CGC GGC ATC CGC ATT AAC CCC GCG GGG CTT CTG GAG ACA      2157
Gly Val Gly Arg Gly Ile Arg Ile Asn Pro Ala Gly Leu Leu Glu Thr
                    70                  75                  80

AAC GAC CTC GCG TCC GCT GTC TTC CCA CCG CTG GCC TCC GAT GAG GCC      2205
Asn Asp Leu Ala Ser Ala Val Phe Pro Pro Leu Ala Ser Asp Glu Ala
                85                  90                  95

GGC AAC GTC ACG CTC AAC ATG TCT GAC GGG CTA TAT ACT AAG GAC AAC      2253
Gly Asn Val Thr Leu Asn Met Ser Asp Gly Leu Tyr Thr Lys Asp Asn
            100                 105                 110

AAG CTA GCT GTC AAA GTA GGT CCC GGG CTG TCC CTC GAC TCC AAT AAT      2301
Lys Leu Ala Val Lys Val Gly Pro Gly Leu Ser Leu Asp Ser Asn Asn
        115                 120                 125

GCT CTC CAG GTC CAC ACA GGC GAC GGG CTC ACG GTA ACC GAT GAC AAG      2349
Ala Leu Gln Val His Thr Gly Asp Gly Leu Thr Val Thr Asp Asp Lys
130                 135                 140                 145

GTG TCT CTA AAT ACC CAA GCT CCC CTC TCG ACC ACC AGC GCG GGC CTC      2397
Val Ser Leu Asn Thr Gln Ala Pro Leu Ser Thr Thr Ser Ala Gly Leu
                150                 155                 160

TCC CTA CTT CTG GGT CCC AGC CTC CAC TTA GGT GAG GAG GAA CGA CTA      2445
Ser Leu Leu Leu Gly Pro Ser Leu His Leu Gly Glu Glu Glu Arg Leu
            165                 170                 175

ACA GTA AAC ACC GGA GCG GGC CTC CAA ATT AGC AAT AAC GCT CTG GCC      2493
Thr Val Asn Thr Gly Ala Gly Leu Gln Ile Ser Asn Asn Ala Leu Ala
        180                 185                 190

GTA AAA GTA GGT TCA GGT ATC ACC GTA GAT GCT CAA AAC CAG CTC GCT      2541
Val Lys Val Gly Ser Gly Ile Thr Val Asp Ala Gln Asn Gln Leu Ala
    195                 200                 205

GCA TCC CTG GGG GAC GGT CTA GAA AGC AGA GAT AAT AAA ACT GTC GTT      2589
Ala Ser Leu Gly Asp Gly Leu Glu Ser Arg Asp Asn Lys Thr Val Val
210                 215                 220                 225

AAG GCT GGG CCC GGA CTT ACA ATA ACT AAT CAA GCT CTT ACT GTT GCT      2637
Lys Ala Gly Pro Gly Leu Thr Ile Thr Asn Gln Ala Leu Thr Val Ala
                230                 235                 240

ACC GGG AAC GGC CTT CAG GTC AAC CCG GAA GGG CAA CTG CAG CTA AAC      2685
Thr Gly Asn Gly Leu Gln Val Asn Pro Glu Gly Gln Leu Gln Leu Asn
            245                 250                 255

ATT ACT GCC GGT CAG GGC CTC AAC TTT GCA AAC AAC AGC CTC GCC GTG      2733
Ile Thr Ala Gly Gln Gly Leu Asn Phe Ala Asn Asn Ser Leu Ala Val
        260                 265                 270

GAG CTG GGC TCG GGC CTG CAT TTT CCC CCT GGC CAA AAC CAA GTA AGC      2781
Glu Leu Gly Ser Gly Leu His Phe Pro Pro Gly Gln Asn Gln Val Ser
    275                 280                 285

CTT TAT CCC GGA GAT GGA ATA GAC ATC CGA GAT AAT AGG GTG ACT GTG      2829
Leu Tyr Pro Gly Asp Gly Ile Asp Ile Arg Asp Asn Arg Val Thr Val
290                 295                 300                 305

CCC GCT GGG CCA GGC CTG AGA ATG CTC AAC CAC CAA CTT GCC GTA GCT      2877
Pro Ala Gly Pro Gly Leu Arg Met Leu Asn His Gln Leu Ala Val Ala
                310                 315                 320

TCC GGA GAC GGT TTA GAA GTC CAC AGC GAC ACC CTC CGG TTA AAG CTC      2925
Ser Gly Asp Gly Leu Glu Val His Ser Asp Thr Leu Arg Leu Lys Leu
            325                 330                 335

TCC CAC GGC CTG ACA TTT GAA AAT GGC GCC GTA CGA GCA AAA CTA GGA      2973
Ser His Gly Leu Thr Phe Glu Asn Gly Ala Val Arg Ala Lys Leu Gly
        340                 345                 350

CCA GGA CTT GGC ACA GAC GAC TCT GGT CGG TCC GTG GTT CGC ACA GGT      3021
Pro Gly Leu Gly Thr Asp Asp Ser Gly Arg Ser Val Val Arg Thr Gly
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    355                 360                 365

CGA GGA CTT AGA GTT GCA AAC GGC CAA GTC CAG ATC TTC AGC GGA AGA     3069
Arg Gly Leu Arg Val Ala Asn Gly Gln Val Gln Ile Phe Ser Gly Arg
370                 375                 380                 385

GGC ACC GCC ATC GGC ACT GAT AGC AGC CTC ACT CTC AAC ATC CGG GCG     3117
Gly Thr Ala Ile Gly Thr Asp Ser Ser Leu Thr Leu Asn Ile Arg Ala
                390                 395                 400

CCC CTA CAA TTT TCT GGA CCC GCC TTG ACT GCT AGT TTG CAA GGC AGT     3165
Pro Leu Gln Phe Ser Gly Pro Ala Leu Thr Ala Ser Leu Gln Gly Ser
            405                 410                 415

GGT CCG ATT ACT TAC AAC AGC AAC AAT GGC ACT TTC GGT CTC TCT ATA     3213
Gly Pro Ile Thr Tyr Asn Ser Asn Asn Gly Thr Phe Gly Leu Ser Ile
        420                 425                 430

GGC CCC GGA ATG TGG GTA GAC CAA AAC AGA CTT CAG GTA AAC CCA GGC     3261
Gly Pro Gly Met Trp Val Asp Gln Asn Arg Leu Gln Val Asn Pro Gly
    435                 440                 445

GCT GGT TTA GTC TTC CAA GGA AAC AAC CTT GTC CCA AAC CTT GCG GAT     3309
Ala Gly Leu Val Phe Gln Gly Asn Asn Leu Val Pro Asn Leu Ala Asp
450                 455                 460                 465

CCG CTG GCT ATT TCC GAC AGC AAA ATT AGT CTC AGT CTC GGT CCC GGC     3357
Pro Leu Ala Ile Ser Asp Ser Lys Ile Ser Leu Ser Leu Gly Pro Gly
                470                 475                 480

CTG ACC CAA GCT TCC AAC GCC CTG ACT TTA AGT TTA GGA AAC GGG CTT     3405
Leu Thr Gln Ala Ser Asn Ala Leu Thr Leu Ser Leu Gly Asn Gly Leu
            485                 490                 495

GAA TTC TCC AAT CAA GCC GTT GCT ATA AAA GCG GGC CGG GGC TTA CGC     3453
Glu Phe Ser Asn Gln Ala Val Ala Ile Lys Ala Gly Arg Gly Leu Arg
        500                 505                 510

TTT GAG TCT TCC TCA CAA GCT TTA GAG AGC AGC CTC ACA GTC GGA AAT     3501
Phe Glu Ser Ser Ser Gln Ala Leu Glu Ser Ser Leu Thr Val Gly Asn
    515                 520                 525

GGC TTA ACG CTT ACC GAT ACT GTG ATC CGC CCC AAC CTA GGG GAC GGC     3549
Gly Leu Thr Leu Thr Asp Thr Val Ile Arg Pro Asn Leu Gly Asp Gly
530                 535                 540                 545

CTA GAG GTC AGA GAC AAT AAA ATC ATT GTT AAG CTG GGC GCG AAT CTT     3597
Leu Glu Val Arg Asp Asn Lys Ile Ile Val Lys Leu Gly Ala Asn Leu
                550                 555                 560

CGT TTT GAA AAC GGA GCC GTA ACC GCC GGC ACC GTT AAC CCT TCT GCG     3645
Arg Phe Glu Asn Gly Ala Val Thr Ala Gly Thr Val Asn Pro Ser Ala
            565                 570                 575

CCC GAG GCA CCA CCA ACT CTC ACT GCA GAA CCA CCC CTC CGA GCC TCC     3693
Pro Glu Ala Pro Pro Thr Leu Thr Ala Glu Pro Pro Leu Arg Ala Ser
        580                 585                 590

AAC TCC CAT CTT CAA CTG TCC CTA TCG GAG GGC TTG GTT GTG CAT AAC     3741
Asn Ser His Leu Gln Leu Ser Leu Ser Glu Gly Leu Val Val His Asn
    595                 600                 605

AAC GCC CTT GCT CTC CAA CTG GGA GAC GGC ATG GAA GTA AAT CAG CAC     3789
Asn Ala Leu Ala Leu Gln Leu Gly Asp Gly Met Glu Val Asn Gln His
610                 615                 620                 625

GGA CTT ACT TTA AGA GTA GGC TCG GGT TTG CAA ATG CGT GAC GGC ATT     3837
Gly Leu Thr Leu Arg Val Gly Ser Gly Leu Gln Met Arg Asp Gly Ile
                630                 635                 640

TTA ACA GTT ACA CCC AGC GGC ACT CCT ATT GAG CCC AGA CTG ACT GCC     3885
Leu Thr Val Thr Pro Ser Gly Thr Pro Ile Glu Pro Arg Leu Thr Ala
            645                 650                 655

CCA CTG ACT CAG ACA GAG AAT GGA ATC GGG CTC GCT CTC GGC GCC GGC     3933
Pro Leu Thr Gln Thr Glu Asn Gly Ile Gly Leu Ala Leu Gly Ala Gly
        660                 665                 670
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TTG GAA TTA GAC GAG AGC GCG CTC CAA GTA AAA GTT GGG CCC GGC ATG     3981
Leu Glu Leu Asp Glu Ser Ala Leu Gln Val Lys Val Gly Pro Gly Met
    675                 680                 685

CGC CTG AAC CCT GTA GAA AAG TAT GTA ACC CTG CTC CTG GGT CCT GGC     4029
Arg Leu Asn Pro Val Glu Lys Tyr Val Thr Leu Leu Leu Gly Pro Gly
690                 695                 700                 705

CTT AGT TTT GGG CAG CCG GCC AAC AGG ACA AAT TAT GAT GTG CGC GTT     4077
Leu Ser Phe Gly Gln Pro Ala Asn Arg Thr Asn Tyr Asp Val Arg Val
                710                 715                 720

TCT GTG GAG CCC CCC ATG GTT TTC GGA CAG CGT GGT CAG CTC ACA TTT     4125
Ser Val Glu Pro Pro Met Val Phe Gly Gln Arg Gly Gln Leu Thr Phe
            725                 730                 735

TTA GTG GGT CAC GGA CTA CAC ATT CAA AAT TCC AAA CTT CAG CTC AAT     4173
Leu Val Gly His Gly Leu His Ile Gln Asn Ser Lys Leu Gln Leu Asn
        740                 745                 750

TTG GGA CAA GGC CTC AGA ACT GAC CCC GTC ACC AAC CAG CTG GAA GTG     4221
Leu Gly Gln Gly Leu Arg Thr Asp Pro Val Thr Asn Gln Leu Glu Val
    755                 760                 765

CCC CTC GGT CAA GGT TTG GAA ATT GCA GAC GAA TCC CAG GTT AGG GTT     4269
Pro Leu Gly Gln Gly Leu Glu Ile Ala Asp Glu Ser Gln Val Arg Val
770                 775                 780                 785

AAA TTG GGC GAT GGC CTG CAG TTT GAT TCA CAA GCT CGC ATC ACT ACC     4317
Lys Leu Gly Asp Gly Leu Gln Phe Asp Ser Gln Ala Arg Ile Thr Thr
                790                 795                 800

GCT CCT AAC ATG GTC ACT GAA ACT CTG TGG ACC GGA ACA GGC AGT AAT     4365
Ala Pro Asn Met Val Thr Glu Thr Leu Trp Thr Gly Thr Gly Ser Asn
            805                 810                 815

GCT AAT GTT ACA TGG CGG GGC TAC ACT GCC CCC GGC AGC AAA CTC TTT     4413
Ala Asn Val Thr Trp Arg Gly Tyr Thr Ala Pro Gly Ser Lys Leu Phe
        820                 825                 830

TTG AGT CTC ACT CGG TTC AGC ACT GGT CTA GTT TTA GGA AAC ATG ACT     4461
Leu Ser Leu Thr Arg Phe Ser Thr Gly Leu Val Leu Gly Asn Met Thr
    835                 840                 845

ATT GAC AGC AAT GCA TCC TTT GGG CAA TAC ATT AAC GCG GGA CAC GAA     4509
Ile Asp Ser Asn Ala Ser Phe Gly Gln Tyr Ile Asn Ala Gly His Glu
850                 855                 860                 865

CAG ATC GAA TGC TTT ATA TTG TTG GAC AAT CAG GGT AAC CTA AAA GAA     4557
Gln Ile Glu Cys Phe Ile Leu Leu Asp Asn Gln Gly Asn Leu Lys Glu
                870                 875                 880

GGA TCT AAC TTG CAA GGC ACT TGG GAA GTG AAG AAC AAC CCC TCT GCT     4605
Gly Ser Asn Leu Gln Gly Thr Trp Glu Val Lys Asn Asn Pro Ser Ala
            885                 890                 895

TCC AAA GCT GCT TTT TTG CCT TCC ACC GCC CTA TAC CCC ATC CTC AAC     4653
Ser Lys Ala Ala Phe Leu Pro Ser Thr Ala Leu Tyr Pro Ile Leu Asn
        900                 905                 910

GAA AGC CGA GGG AGT CTT CCT GGA AAA AAT CTT GTG GGC ATG CAA GCC     4701
Glu Ser Arg Gly Ser Leu Pro Gly Lys Asn Leu Val Gly Met Gln Ala
    915                 920                 925

ATA CTG GGA GGC GGG GGC ACT TGC ACT GTG ATA GCC ACC CTC AAT GGC     4749
Ile Leu Gly Gly Gly Gly Thr Cys Thr Val Ile Ala Thr Leu Asn Gly
930                 935                 940                 945

AGA CGC AGC AAC AAC TAT CCC GCG GGC CAG TCC ATA ATT TTC GTG TGG     4797
Arg Arg Ser Asn Asn Tyr Pro Ala Gly Gln Ser Ile Ile Phe Val Trp
                950                 955                 960

CAA GAA TTC AAC ACC ATA GCC CGC CAA CCT CTG AAC CAC TCT ACA CTT     4845
Gln Glu Phe Asn Thr Ile Ala Arg Gln Pro Leu Asn His Ser Thr Leu
            965                 970                 975

ACT TTT TCT TAC TGG ACT TAAATAAGTT GGAAATAAAG AGTTAAACTG           4893
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Thr Phe Ser Tyr Trp Thr
980

AATGTTTAAG TGCAACAGAC TTTTATTGGT TTTGGCTCAC AACAAATTAC AACAGCATAG 4953

ACAAGTCATA CCGGTCAAAC AACACAGGCT CTCGAAAACG GGCTAACCGC TCCAAGAATC 5013

TGTCACGCAG ACGAGCAAGT CCTAAATGTT TTTTCACTCT CTTCGGGGCC AAGTTCAGCA 5073

TGTATCGGAT TTTCTGCTTA CACCTTT 5100

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 983 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Ser His Pro Pro Val Asn Ile Met Lys Arg Ser Val Pro Gln Asp Phe
1 5 10 15

Asn Leu Val Tyr Pro Tyr Lys Ala Lys Arg Pro Asn Ile Met Pro Pro
20 25 30

Phe Phe Asp Arg Asn Gly Phe Val Glu Asn Gln Glu Ala Thr Leu Ala
35 40 45

Met Leu Val Glu Lys Pro Leu Thr Phe Asp Lys Glu Gly Ala Leu Thr
50 55 60

Leu Gly Val Gly Arg Gly Ile Arg Ile Asn Pro Ala Gly Leu Leu Glu
65 70 75 80

Thr Asn Asp Leu Ala Ser Ala Val Phe Pro Pro Leu Ala Ser Asp Glu
85 90 95

Ala Gly Asn Val Thr Leu Asn Met Ser Asp Gly Leu Tyr Thr Lys Asp
100 105 110

Asn Lys Leu Ala Val Lys Val Gly Pro Gly Leu Ser Leu Asp Ser Asn
115 120 125

Asn Ala Leu Gln Val His Thr Gly Asp Gly Leu Thr Val Thr Asp Asp
130 135 140

Lys Val Ser Leu Asn Thr Gln Ala Pro Leu Ser Thr Thr Ser Ala Gly
145 150 155 160

Leu Ser Leu Leu Leu Gly Pro Ser Leu His Leu Gly Glu Glu Glu Arg
165 170 175

Leu Thr Val Asn Thr Gly Ala Gly Leu Gln Ile Ser Asn Asn Ala Leu
180 185 190

Ala Val Lys Val Gly Ser Gly Ile Thr Val Asp Ala Gln Asn Gln Leu
195 200 205

Ala Ala Ser Leu Gly Asp Gly Leu Glu Ser Arg Asp Asn Lys Thr Val
210 215 220

Val Lys Ala Gly Pro Gly Leu Thr Ile Thr Asn Gln Ala Leu Thr Val
225 230 235 240

Ala Thr Gly Asn Gly Leu Gln Val Asn Pro Glu Gly Gln Leu Gln Leu
245 250 255

Asn Ile Thr Ala Gly Gln Gly Leu Asn Phe Ala Asn Asn Ser Leu Ala
260 265 270

Val Glu Leu Gly Ser Gly Leu His Phe Pro Pro Gly Gln Asn Gln Val
275 280 285

Ser Leu Tyr Pro Gly Asp Gly Ile Asp Ile Arg Asp Asn Arg Val Thr
290 295 300

Val Pro Ala Gly Pro Gly Leu Arg Met Leu Asn His Gln Leu Ala Val
305 310 315 320

Ala Ser Gly Asp Gly Leu Glu Val His Ser Asp Thr Leu Arg Leu Lys
325 330 335

Leu Ser His Gly Leu Thr Phe Glu Asn Gly Ala Val Arg Ala Lys Leu
340 345 350

Gly Pro Gly Leu Gly Thr Asp Asp Ser Gly Arg Ser Val Val Arg Thr
355 360 365

Gly Arg Gly Leu Arg Val Ala Asn Gly Gln Val Gln Ile Phe Ser Gly
370 375 380

Arg Gly Thr Ala Ile Gly Thr Asp Ser Ser Leu Thr Leu Asn Ile Arg
385 390 395 400

Ala Pro Leu Gln Phe Ser Gly Pro Ala Leu Thr Ala Ser Leu Gln Gly
405 410 415

Ser Gly Pro Ile Thr Tyr Asn Ser Asn Asn Gly Thr Phe Gly Leu Ser
420 425 430

Ile Gly Pro Gly Met Trp Val Asp Gln Asn Arg Leu Gln Val Asn Pro
435 440 445

Gly Ala Gly Leu Val Phe Gln Gly Asn Asn Leu Val Pro Asn Leu Ala
450 455 460

Asp Pro Leu Ala Ile Ser Asp Ser Lys Ile Ser Leu Ser Leu Gly Pro
465 470 475 480

Gly Leu Thr Gln Ala Ser Asn Ala Leu Thr Leu Ser Leu Gly Asn Gly
485 490 495

Leu Glu Phe Ser Asn Gln Ala Val Ala Ile Lys Ala Gly Arg Gly Leu
500 505 510

Arg Phe Glu Ser Ser Ser Gln Ala Leu Glu Ser Ser Leu Thr Val Gly
515 520 525

Asn Gly Leu Thr Leu Thr Asp Thr Val Ile Arg Pro Asn Leu Gly Asp
530 535 540

Gly Leu Glu Val Arg Asp Asn Lys Ile Ile Val Lys Leu Gly Ala Asn
545 550 555 560

Leu Arg Phe Glu Asn Gly Ala Val Thr Ala Gly Thr Val Asn Pro Ser
565 570 575

Ala Pro Glu Ala Pro Pro Thr Leu Thr Ala Glu Pro Pro Leu Arg Ala
580 585 590

Ser Asn Ser His Leu Gln Leu Ser Leu Ser Glu Gly Leu Val Val His
595 600 605

Asn Asn Ala Leu Ala Leu Gln Leu Gly Asp Gly Met Glu Val Asn Gln
610 615 620

His Gly Leu Thr Leu Arg Val Gly Ser Gly Leu Gln Met Arg Asp Gly
625 630 635 640

Ile Leu Thr Val Thr Pro Ser Gly Thr Pro Ile Glu Pro Arg Leu Thr
645 650 655

Ala Pro Leu Thr Gln Thr Glu Asn Gly Ile Gly Leu Ala Leu Gly Ala
660 665 670

Gly Leu Glu Leu Asp Glu Ser Ala Leu Gln Val Lys Val Gly Pro Gly
675 680 685

Met Arg Leu Asn Pro Val Glu Lys Tyr Val Thr Leu Leu Leu Gly Pro
690 695 700

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Gly Leu Ser Phe Gly Gln Pro Ala Asn Arg Thr Asn Tyr Asp Val Arg
705                 710                 715                 720

Val Ser Val Glu Pro Pro Met Val Phe Gly Gln Arg Gly Gln Leu Thr
                725                 730                 735

Phe Leu Val Gly His Gly Leu His Ile Gln Asn Ser Lys Leu Gln Leu
            740                 745                 750

Asn Leu Gly Gln Gly Leu Arg Thr Asp Pro Val Thr Asn Gln Leu Glu
        755                 760                 765

Val Pro Leu Gly Gln Gly Leu Glu Ile Ala Asp Glu Ser Gln Val Arg
    770                 775                 780

Val Lys Leu Gly Asp Gly Leu Gln Phe Asp Ser Gln Ala Arg Ile Thr
785                 790                 795                 800

Thr Ala Pro Asn Met Val Thr Glu Thr Leu Trp Thr Gly Thr Gly Ser
                805                 810                 815

Asn Ala Asn Val Thr Trp Arg Gly Tyr Thr Ala Pro Gly Ser Lys Leu
            820                 825                 830

Phe Leu Ser Leu Thr Arg Phe Ser Thr Gly Leu Val Leu Gly Asn Met
        835                 840                 845

Thr Ile Asp Ser Asn Ala Ser Phe Gly Gln Tyr Ile Asn Ala Gly His
    850                 855                 860

Glu Gln Ile Glu Cys Phe Ile Leu Leu Asp Asn Gln Gly Asn Leu Lys
865                 870                 875                 880

Glu Gly Ser Asn Leu Gln Gly Thr Trp Glu Val Lys Asn Asn Pro Ser
                885                 890                 895

Ala Ser Lys Ala Ala Phe Leu Pro Ser Thr Ala Leu Tyr Pro Ile Leu
            900                 905                 910

Asn Glu Ser Arg Gly Ser Leu Pro Gly Lys Asn Leu Val Gly Met Gln
        915                 920                 925

Ala Ile Leu Gly Gly Gly Gly Thr Cys Thr Val Ile Ala Thr Leu Asn
    930                 935                 940

Gly Arg Arg Ser Asn Asn Tyr Pro Ala Gly Gln Ser Ile Ile Phe Val
945                 950                 955                 960

Trp Gln Glu Phe Asn Thr Ile Ala Arg Gln Pro Leu Asn His Ser Thr
                965                 970                 975

Leu Thr Phe Ser Tyr Trp Thr
            980
```

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 227 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

```
Met Ser Lys Glu Ile Pro Thr Pro Tyr Met Trp Ser Tyr Gln Pro Gln
1               5                   10                  15

Met Gly Leu Ala Ala Gly Ala Ala Gln Asp Tyr Ser Thr Arg Ile Asn
            20                  25                  30

Tyr Met Ser Ala Gly Pro His Met Ile Ser Arg Val Asn Gly Ile Arg
        35                  40                  45
```

```
Ala His Arg Asn Arg Ile Leu Leu Glu Gln Ala Ala Ile Thr Thr Thr
    50                  55                  60

Pro Arg Asn Asn Leu Asn Pro Arg Ser Trp Pro Ala Ala Leu Val Tyr
65                  70                  75                  80

Gln Glu Ser Pro Ala Pro Thr Thr Val Val Leu Pro Arg Asp Ala Gln
                85                  90                  95

Ala Glu Val Gln Met Thr Asn Ser Gly Ala Gln Leu Ala Gly Gly Phe
            100                 105                 110

Arg His Arg Val Arg Ser Pro Gly Gln Gly Ile Thr His Leu Lys Ile
        115                 120                 125

Arg Gly Arg Gly Ile Gln Leu Asn Asp Glu Ser Val Ser Ser Ser Leu
    130                 135                 140

Gly Leu Arg Pro Asp Gly Thr Phe Gln Ile Gly Gly Ala Gly Arg Ser
145                 150                 155                 160

Ser Phe Thr Pro Arg Gln Ala Ile Leu Thr Leu Gln Thr Ser Ser Ser
                165                 170                 175

Glu Pro Arg Ser Gly Gly Ile Gly Thr Leu Gln Phe Ile Glu Glu Phe
            180                 185                 190

Val Pro Ser Val Tyr Phe Asn Pro Phe Ser Gly Pro Pro Gly His Tyr
        195                 200                 205

Pro Asp Gln Phe Ile Pro Asn Phe Asp Ala Val Lys Asp Ser Ala Asp
    210                 215                 220

Gly Tyr Asp
225
```

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 128 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```
Met Thr Asp Thr Leu Asp Leu Glu Met Asp Gly Ile Ile Thr Glu Gln
1               5                   10                  15

Arg Leu Leu Glu Arg Arg Arg Ala Ala Ala Glu Gln Gln Arg Met Asn
            20                  25                  30

Gln Glu Leu Gln Asp Met Val Asn Leu His Gln Cys Lys Arg Gly Ile
        35                  40                  45

Phe Cys Leu Val Lys Gln Ala Lys Val Thr Tyr Asp Ser Asn Thr Thr
    50                  55                  60

Gly His Arg Leu Ser Tyr Lys Leu Pro Thr Lys Arg Gln Lys Leu Val
65                  70                  75                  80

Val Met Val Gly Glu Lys Pro Ile Thr Ile Thr Gln His Ser Val Glu
                85                  90                  95

Thr Glu Gly Cys Ile His Ser Pro Cys Gln Gly Pro Glu Asp Leu Cys
            100                 105                 110

Thr Leu Ile Lys Thr Leu Cys Gly Leu Lys Asp Leu Ile Pro Phe Asn
        115                 120                 125
```

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 582 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Met Lys Arg Ala Arg Pro Ser Glu Asp Thr Phe Asn Pro Val Tyr Pro
1 5 10 15

Tyr Asp Thr Glu Thr Gly Pro Pro Thr Val Pro Phe Leu Thr Pro Pro
20 25 30

Phe Val Ser Pro Asn Gly Phe Gln Glu Ser Pro Pro Gly Val Leu Ser
35 40 45

Leu Arg Val Ser Glu Pro Leu Asp Thr Ser His Gly Met Leu Ala Leu
50 55 60

Lys Met Gly Ser Gly Leu Thr Leu Asp Lys Ala Gly Asn Leu Thr Ser
65 70 75 80

Gln Asn Val Thr Thr Val Thr Gln Pro Leu Lys Lys Thr Lys Ser Asn
85 90 95

Ile Ser Leu Asp Thr Ser Ala Pro Leu Thr Ile Thr Ser Gly Ala Leu
100 105 110

Thr Val Ala Thr Thr Ala Pro Leu Ile Val Thr Ser Gly Ala Leu Ser
115 120 125

Val Gln Ser Gln Ala Pro Leu Thr Val Gln Asp Ser Lys Leu Ser Ile
130 135 140

Ala Thr Lys Gly Pro Ile Thr Val Ser Asp Gly Lys Leu Ala Leu Gln
145 150 155 160

Thr Ser Ala Pro Leu Ser Gly Ser Asp Ser Asp Thr Leu Thr Val Thr
165 170 175

Ala Ser Pro Pro Leu Thr Thr Ala Thr Gly Ser Leu Gly Ile Asn Met
180 185 190

Glu Asp Pro Ile Tyr Val Asn Asn Gly Lys Ile Gly Ile Lys Ile Ser
195 200 205

Gly Pro Leu Gln Val Ala Gln Asn Ser Asp Thr Leu Thr Val Val Thr
210 215 220

Gly Pro Gly Val Thr Val Glu Gln Asn Ser Leu Arg Thr Lys Val Ala
225 230 235 240

Gly Ala Ile Gly Tyr Asp Ser Ser Asn Asn Met Glu Ile Lys Thr Gly
245 250 255

Gly Gly Met Arg Ile Asn Asn Asn Leu Leu Ile Leu Asp Val Asp Tyr
260 265 270

Pro Phe Asp Ala Gln Thr Lys Leu Arg Leu Lys Leu Gly Gln Gly Pro
275 280 285

Leu Tyr Ile Asn Ala Ser His Asn Leu Asp Ile Asn Tyr Asn Arg Gly
290 295 300

Leu Tyr Leu Phe Asn Ala Ser Asn Asn Thr Lys Lys Leu Glu Val Ser
305 310 315 320

Ile Lys Lys Ser Ser Gly Leu Asn Phe Asp Asn Thr Ala Ile Ala Ile
325 330 335

Asn Ala Gly Lys Gly Leu Glu Phe Asp Thr Asn Thr Ser Glu Ser Pro
340 345 350

Asp Ile Asn Pro Ile Lys Thr Lys Ile Gly Ser Gly Ile Asp Tyr Asn
355 360 365

Glu Asn Gly Ala Met Ile Thr Lys Leu Gly Ala Gly Leu Ser Phe Asp
370 375 380

Asn Ser Gly Ala Ile Thr Ile Gly Asn Lys Asn Asp Asp Lys Leu Thr
385 390 395 400

Leu Trp Thr Thr Pro Asp Pro Ser Pro Asn Cys Arg Ile His Ser Asp
405 410 415

Asn Asp Cys Lys Phe Thr Leu Val Leu Thr Lys Cys Gly Ser Gln Val
420 425 430

Leu Ala Thr Val Ala Ala Leu Ala Val Ser Gly Asp Leu Ser Ser Met
435 440 445

Thr Gly Thr Val Ala Ser Val Ser Ile Phe Leu Arg Phe Asp Gln Asn
450 455 460

Gly Val Leu Met Glu Asn Ser Ser Leu Lys Lys His Tyr Trp Asn Phe
465 470 475 480

Arg Asn Gly Asn Ser Thr Asn Ala Asn Pro Tyr Thr Asn Ala Val Gly
485 490 495

Phe Met Pro Asn Leu Leu Ala Tyr Pro Lys Thr Gln Ser Gln Thr Ala
500 505 510

Lys Asn Asn Ile Val Ser Gln Val Tyr Leu His Gly Asp Lys Thr Lys
515 520 525

Pro Met Ile Leu Thr Ile Thr Leu Asn Gly Thr Ser Glu Ser Thr Glu
530 535 540

Thr Ser Glu Val Ser Thr Tyr Ser Met Ser Phe Thr Trp Ser Trp Glu
545 550 555 560

Ser Gly Lys Tyr Thr Thr Glu Thr Phe Ala Thr Asn Ser Tyr Thr Phe
565 570 575

Ser Tyr Ile Ala Gln Glu
580

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION: /note= "This position is X2."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 4
(D) OTHER INFORMATION: /note= "This position is X13."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(D) OTHER INFORMATION: /note= "This position is X2."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Cys Xaa Cys Xaa Cys Xaa Cys
1 5

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

Gln Ser Ser Xaa Ser Thr Ser
1 5

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Pro Leu Leu Phe Ala Phe Val Leu Cys Thr Gly Cys Ala Val Leu Leu
1 5 10 15

Thr Ala Phe Gly Pro Ser Ile Leu Ser Gly Thr
20 25

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 57 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Glu Glu Val Thr Ser His Phe Phe Leu Asp Cys Pro Glu Asp Pro Ser
1 5 10 15

Arg Glu Cys Ser Ser Cys Gly Phe His Gln Ala Gln Ser Gly Ile Pro
20 25 30

Gly Ile Met Cys Ser Leu Cys Tyr Met Arg Gln Thr Tyr His Cys Ile
35 40 45

Tyr Ser Pro Val Ser Glu Glu Glu Met
50 55

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Val Asp Leu Glu Cys His Glu Val Leu Pro Pro Ser
1 5 10

Claims

1. A live recombinant bovine adenovirus vector (BAV) system selected from the group consisting of:

(a) a system wherein part or all of the E1 gene region is replaced by a heterologous nucleotide sequence encoding a foreign gene or fragment thereof;

(b) a system wherein a part or all of the E3 gene region is replaced by a heterologous nucleotide sequence encoding a foreign gene or fragment thereof; and

(c) a system wherein part or all of the E1 gene region and part or all of the E3 gene region are deleted and a heterologous nucleotide sequence encoding a foreign gene or fragment thereof is inserted into at least one of the deletions.

2. The BAV system of claim 1 which is a bovine adenovirus type 3.

3. The BAV system of claim 1 wherein (a) a recombinant BAV wherein part or all of the E1 gene region is replaced by a heterologous nucleotide sequence encoding a foreign gene or fragment thereof.

4. The BAV system of claim 1 wherein (b) a recombinant BAV wherein a part or all of the E3 gene region is replaced by a heterologous nucleotide sequence encoding a foreign gene or fragment thereof.

5. The BAV system of claim 1 wherein the foreign nucleotide sequence is with or without the control of an exogenous promoter.

6. The BAV system of claim 1 wherein (c) a system wherein part or all of the E1 gene region and part or all of the E3 gene region are deleted and a

heterologous nucleotide sequence encoding a foreign gene or fragment thereof is inserted into at least one of the deletions.

7. A recombinant vector system comprising the entire BAV genome and a plasmid capable of generating a recombinant virus by in vivo recombination following cotransfection of a suitable cell line comprising the entire BAV genome representing the wild-type BAV genome and a plasmid comprising an adenovirus left end nucleotide sequences containing the E1A gene region or a plasmid comprising adenovirus right end sequences containing the E3 gene region, the plasmid with a heterologous nucleotide sequence encoding a foreign gene or fragment thereof substituted for part or all of the E1 and/or E3 gene regions, respectively.

8. A recombinant bovine adenovirus vector system comprising two plasmids capable of generating a recombinant virus by in vivo recombination following cotransfection of a cell line comprising

(1) a first plasmid comprising the entire BAV genome except for a deletion of part or all of the E1 and/or E3 gene regions, and

(2) a second plasmid comprising BAV left or right end nucleotide sequences containing the E1 or E3 gene regions, respectively, having a heterologous nucleotide sequence encoding a foreign gene or fragment thereof inserted for the deletion of a part or all of the E1 or E3 gene regions.

9. A live viable recombinant bovine adenovirus (BAV) comprising a deletion of part or all of the E1 gene region, a deletion of part or all of the E3 gene region or deletion of both, and inserted into at least one deletion a heterologous nucleotide sequence coding for a polypeptide or an antigenic determinant produced by a disease causing organism.

10. A live viable recombinant bovine adenovirus (BAV) for producing an immune response in a mammalian host comprising:

(1) a live bovine adenovirus (BAV) modified to contain a heterologous nucleotide sequence coding for a polypeptide or an antigenic determinant corresponding to the desired immune response in association with or without

(2) an effective promoter for said nucleotide sequence to provide expression of said antigenic determinant in immunogenic non-pathogenic quantities.

11. A live recombinant bovine adenovirus expression system comprising a deletion of all or part of the E1 gene region or all or part of the E3 gene region, or both deletions and inserted in at least one deletion a heterologous nucleotide sequence coding for a foreign gene or fragment thereof under control of an expression promoter with or without one or more polyadenylation signal.

12. A recombinant mammalian cell line comprising bovine adenovirus (BAV) E1 gene region, said recombinant cell line thereby capable of allowing replication therein of a bovine adenovirus comprising an E1 deletion which may or may not be replaced by a heterologous or homologous nucleotide sequence encoding a foreign gene or fragment thereof.

13. The cell line of claim 12 which is a bovine cell line.

14. The recombinant mammalian cell line of claim 12 wherein the heterologous or homologous nucleotide sequence encoding the foreign gene or fragment thereof is selected from the group consisting of a bovine adenovirus (BAV) E1 polypeptide,, a BAV

E1-associated polypeptide, a growth factor, a cellular receptor or other cellular polypeptide.

15. A recombinant mammalian cell line comprising bovine adenovirus E1 genes, said recombinant cell line thereby capable of allowing DNA-mediated transfection to generate a recombinant bovine adenovirus (BAV) selected from the group consisting of:

(a) a recombinant BAV wherein part or all of the E1 gene region is replaced by a heterologous nucleotide sequence encoding a foreign gene or fragment thereof,

(b) a recombinant BAV wherein part or all of the E3 gene region is replaced by a heterologous nucleotide sequence encoding a foreign gene or fragment thereof,

(c) a recombinant BAV wherein part or all of the E1 gene region and part or all of the E3 gene region are deleted and inserted into at least one deletion a heterologous nucleotide sequence encoding a foreign gene or fragment thereof,

(d) a recombinant BAV wherein part or all of the E1 gene region and/or part or all of the E3 gene region are deleted and inserted into at least one deletion a heterologous nucleotide sequence encoding more than one foreign gene or fragment thereof to produce a recombinant fusion protein, and

(e) a mutant BAV wherein part or all of the E1 gene region and/or part or all of the E3 gene region are deleted.

16. A method of preparing a recombinant polypeptide or fragment thereof which comprises:

(1) infecting the mammalian cell line of claim 12, with a recombinant bovine adenovirus comprising a deletion of part or all of the E1 gene region and/or part or all of the E3 gene region and inserted into at least one deletion a heterologous

nucleotide sequence encoding the polypeptide or fragment thereof,

(2) replicating the recombinant virus in a recombinant cell line under conditions to provide for expression of the polypeptide, and

(3) recovering the recombinant polypeptide or antigenic fragment thereof.

17. A method of isolating a polypeptide which comprises:

(1) replicating a recombinant mammalian cell line of claim 12 under conditions to provide for expression of the polypeptide, and

(2) recovering the polypeptide or fragment thereof.

18. A method for eliciting an immune response in a mammalian host to protect against an infection comprising:

administering a vaccine composition comprising a live recombinant BAV of claim 1 wherein the foreign gene or fragment encodes an antigen with or without a pharmaceutically acceptable carrier.

19. A method for eliciting an immune response in a mammalian host to protect against an infection comprising:

administering a vaccine comprising a recombinant polypeptide or fragment thereof prepared by a method of claim 16 with or without a pharmaceutically acceptable carrier.

20. A vaccine for protecting a mammalian host against infection comprising a live recombinant adenovirus of claim 1 wherein the foreign gene or fragment encodes an antigen with or without a pharmaceutically acceptable carrier.

21. A vaccine for protecting a mammalian host against infection comprising a recombinant antigen prepared by a method of claim 16 with or without a pharmaceutically acceptable carrier.

22. A mutant bovine adenovirus (BAV) comprising a deletion of part or all of E1 and/or a deletion of part or all of E3.

23. A method for providing gene therapy to a mammal in need thereof to control a gene deficiency which comprises administering to said mammal a live recombinant bovine adenovirus containing a foreign nucleotide sequence encoding a non-defective form of said gene under conditions wherein the recombinant virus vector genome is incorporated into said mammalian genome or is maintained independently and extrachromosomally to provide expression of the required gene in the target organ or tissue.

```
        10         20         30         40         50         60
CATCATCAAT AATCTACAGT ACACTGATGG CAGCGGTCCA ACTGCCAATC ATTTTTGCCA

        70         80         90        100        110        120
CGTCATTTAT GACGCAACGA CGGCGAGCGT GGCGTGCTGA CGTAACTGTG GGGCGGAGCG

       130        140        150        160        170        180
CGTCGCGGAG GCGGCGGCGC TGGGCGGGGC TGAGGGCGGC GGGGGCGGCG CGCGGGGCGG

       190        200        210        220        230        240
CGCGCGGGGC GGGGCGAGGG GCGGAGTTCC GCACCCGCTA CGTCATTTTC AGACATTTTT

       250        260        270        280        290        300
TAGCAAATTT GCGCCTTTTG CAAGCATTTT TCTCACATTT CAGGTATTTA GAGGGCGGAT

       310        320        330        340        350        360
TTTTGGTGTT CGTACTTCCG TGTCACATAG TTCACTGTCA ATCTTCATTA CGGCTTAGAC

       370        380        390        400        410        420
AAATTTTCGG CGTCTTTTCC GGGTTTATGT CCCCGGTCAC CTTTATGACT GTGTGAAACA

       430        440        450        460        470        480
CACCTGCCCA TTGTTTACCC TTGGTCAGTT TTTTCGTCTC CTAGGGTGGG AACATCAAGA
```

FIG. 1A

```
       490         500         510         520         530         540
ACAAATTTGC CGAGTAATTG TGCACCTTTT TCCGCGTTAG GACTGCGTTT CACACGTAGA

       550         560         570         580         590         600
CAGACTTTTT CTCATTTTCT CACACTCCGT CGTCCGCTTC AGAGCTCTGC GTCTTCGCTG

         610         620         630         640         650
CCACC ATG AAG TAC CTG GTC CTC GTT CTC AAC GAC GGC ATG AGT CGA ATT GAA
      Met Lys Tyr Leu Val Leu Val Leu Asn Asp Gly Met Ser Arg Ile Glu

       660         670         680         690         700
AAA GCT CTC CTG TGC AGC GAT GGT GAG GTG GAT TTA GAG TGT CAT GAG GTA
Lys Ala Leu Leu Cys Ser Asp Gly Glu Val Asp Leu Glu Cys His Glu Val

     710         720         730         740         750
CTT CCC CCT TCT CCC GCG CCT GTC CCC GCT TCT GTG TCA CCC GTG AGG AGT
Leu Pro Pro Ser Pro Ala Pro Val Pro Ala Ser Val Ser Pro Val Arg Ser

   760         770         780         790         800
CCT CCT CCT CTG TCT CCG GTG TTT CCT CCG TCT CCG CCA GCC CCG CTT GTG
Pro Pro Pro Leu Ser Pro Val Phe Pro Pro Ser Pro Pro Ala Pro Leu Val

  810         820         830         840         850
AAT CCA GAG GCG AGT TCG CTG CTG CAG CAG TAT CGG AGA GAG CTG TTA GAG
Asn Pro Glu Ala Ser Ser Leu Leu Gln Gln Tyr Arg Arg Glu Leu Leu Glu
```

FIG. 1B

```
860             870             880             890             900
AGG AGC CTG CTC CGA ACG GCC GAA GGT CAG CAG CGT GCA GTG TGT CCA TGT
Arg Ser Leu Leu Arg Thr Ala Glu Gly Gln Gln Arg Ala Val Cys Pro Cys

910             920             930             940             950
GAG CGG TTG CCC GTG GAA GAG GAT GAG TGT CTG AAT GCC GTA AAT TTG CTG
Glu Arg Leu Pro Val Glu Glu Asp Glu Cys Leu Asn Ala Val Asn Leu Leu

960             970             980             990            1000            1010
TTT CCT GAT CCC TGG CTA AAT GCA GCT GAA AAT GGG GGT GAT ATT TTT AAG
Phe Pro Asp Pro Trp Leu Asn Ala Ala Glu Asn Gly Gly Asp Ile Phe Lys

          1020            1030            1040            1050            1060
TCT CCG GCT ATG TCT CCA GAA CCG TGG ATA GAT TTG TCT AGC TAC GAT AGC
Ser Pro Ala Met Ser Pro Glu Pro Trp Ile Asp Leu Ser Ser Tyr Asp Ser

        1070            1080            1090            1100            1110
GAT GTA GAA GAG GTG ACT AGT CAC TTT TTT CTG GAT TGC CCT GAA GAC CCC
Asp Val Glu Glu Val Thr Ser His Phe Phe Leu Asp Cys Pro Glu Asp Pro

      1120            1130            1140            1150            1160
AGT CGG GAG TGT TCA TCT TGT GGG TTT CAT CAG GCT CAA AGC GGA ATT CCA
Ser Arg Glu Cys Ser Ser Cys Gly Phe His Gln Ala Gln Ser Gly Ile Pro
```

FIG. IC

```
     1170          1180          1190          1200          1210
GGC ATT ATG TGC AGT TTG TGC TAC ATG CGC CAA ACC TAC CAT TGC ATC TAT
Gly Ile Met Cys Ser Leu Cys Tyr Met Arg Gln Thr Tyr His Cys Ile Tyr

   1220        1230        1240        1250        1260        1270
A[GTAAG TACATTCTGT AAAAGAACAT CTTGGTGATT TCTAGGTATT GTTTAGGGAT
S

      1280        1290        1300        1310        1320          1330
TAACTGGGTG GAGTGATCTT AATCCGGCAT AACCAAATAC ATGTTTTCAC AG]GT CCA GTT
                                                          er Pro Val

         1340        1350        1360        1370        1380        1390
TCT GAA GAG GAA ATG TGAGT CATGTTGACT TTGGCGCGC A AGAGGAAATG TGAGTCATGT
Ser Glu Glu Glu Met End

      1400        1410        1420        1430        1440        1450
TGACTTTGGC GCGCCCTACG GTGACTTTAA AGCAATTTGA GGATCACTTT TTTGTTAGTC

      1460        1470          1480          1490          1500
GCTATAAAGT AGTCACGGAG TCTTC ATG GAT CAC TTA AGC GTT CTT TTG GAT TTG
                               Met Asp His Leu Ser Val Leu Leu Asp Leu

  1510          1520          1530          1540          1550
AAG CTG CTT CGC TCT ATC GTA GCG GGG GCT TCA AAT CGC ACT GGA GTG TGG
Lys Leu Leu Arg Ser Ile Val Ala Gly Ala Ser Asn Arg Thr Gly Val Trp
```

FIG. ID

```
 1560          1570          1580          1590          1600
AAG AGG CGG CTG TGG CTG GGA CGC CTG ACT CAA CTG GTC CAT GAT ACC TGC
Lys Arg Arg Leu Trp Leu Gly Arg Leu Thr Gln Leu Val His Asp Thr Cys

1610          1620          1630          1640          1650
GTA GAG AAC GAG AGC ATA TTT CTC AAT TCT CTG CCA GGG AAT GAA GCT TTT
Val Glu Asn Glu Ser Ile Phe Leu Asn Ser Leu Pro Gly Asn Glu Ala Phe

1660          1670          1680          1690          1700
TTA AGG TTG CTT CGG AGC GGC TAT TTT GAA GTG TTT GAC GTG TTT GTG GTG
Leu Arg Leu Leu Arg Ser Gly Tyr Phe Glu Val Phe Asp Val Phe Val Val

1710          1720          1730          1740          1750          1760
CCT GAG CTG CAT CTG GAC ACT CCG GGT CGA GTG GTC GCC GCT CTT GCT CTG
Pro Glu Leu His Leu Asp Thr Pro Gly Arg Val Val Ala Ala Leu Ala Leu

          1770          1780          1790          1800          1810
CTG GTG TTC ATC CTC AAC GAT TTA GAC GCT AAT TCT GCT TCT TCA GGC TTT
Leu Val Phe Ile Leu Asn Asp Leu Asp Ala Asn Ser Ala Ser Ser Gly Phe

     1820          1830          1840          1850          1860
GAT TCA GGT TTT CTC GTG GAC CGT CTC TGC GTG CCG CTA TGG CTG AAG GCC
Asp Ser Gly Phe Leu Val Asp Arg Leu Cys Val Pro Leu Trp Leu Lys Ala
                                                  Met Ala Glu Gly
```

FIG. 1E

```
      1870          1880          1890          1900          1910
AGG GCG TTC AAG ATC ACC CAG AGC TCC AGG AGC ACT TCG CAG CCT TCC TCG
 Arg Ala Phe Lys Ile Thr Gln Ser Ser Arg Ser Thr Ser Gln Pro Ser Ser
Gln Gly Val Gln Asp His Pro Glu Leu Gln Glu His Phe Ala Ala Phe Leu

      1920          1930          1940          1950          1960
TCG CCC GAC AAG ACG ACC CAG ACT ACC AGC CAG TA GAC GGG GAC AGC CCA
 Ser Pro Asp Lys Thr Thr Gln Thr Thr Ser Gln End
Val Ala Arg Gln Asp Asp Pro Asp Tyr Gln Pro Val Asp Gly Asp Ser Pro

      1970          1980          1990          2000          2010
CCC CGG GCT AGC CTG GAG GAG GCT GAA CAG AGC AGC ACT CGT TTC GAG CAC
 Pro Arg Ala Ser Leu Glu Glu Ala Glu Gln Ser Ser Thr Arg Phe Glu His

   2020          2030          2040          2050          2060
ATC AGT TAC CGA GAC GTG GTG GAT GAC TTC AAT AGA TGC CAT GAT GTT TTT
 Ile Ser Tyr Arg Asp Val Val Asp Asp Phe Asn Arg Cys His Asp Val Phe

  2070          2080          2090          2100          2110
TAT GAG AGG TAC AGT TTT GAG GAC ATA AAG AGC TAC GAG GCT TTG CCT GAG
Tyr Glu Arg Tyr Ser Phe Glu Asp Ile Lys Ser Tyr Glu Ala Leu Pro Glu
```

FIG. IF

```
 2120          2130          2140          2150          2160
GAC AAT TTG GAG CAG CTC ATA GCT ATG CAT GCT AAA ATC AAG CTG CTG CCC
Asp Asn Leu Glu Gln Leu Ile Ala Met His Ala Lys Ile Lys Leu Leu Pro

2170          2180          2190          2200          2210
GGT CGG GAG TAT GAG TTG ACT CAA CCT TTG AAC ATA ACA TCT TGC GCC TAT
Gly Arg Glu Tyr Glu Leu Thr Gln Pro Leu Asn Ile Thr Ser Cys Ala Tyr

2220          2230          2240          2250          2260
GTG CTC GGA AAT GGG GCT ACT ATT AGG GTA ACA GGG GAA GCC TCC CCG GCT
Val Leu Gly Asn Gly Ala Thr Ile Arg Val Thr Gly Glu Ala Ser Pro Ala

2270          2280          2290          2300          2310          2320
ATT AGA GTG GGG GCC ATG GCC GTG GGT CCG TGT GTA ACA GGA ATG ACT GGG
Ile Arg Val Gly Ala Met Ala Val Gly Pro Cys Val Thr Gly Met Thr Gly

          2330          2340          2350          2360          2370
GTG ACT TTT GTG AAT TGT AGG TTT GAG AGA GAG TCA ACA ATT AGG GGG TCC
Val Thr Phe Val Asn Cys Arg Phe Glu Arg Glu Ser Thr Ile Arg Gly Ser

          2380          2390          2400          2410          2420
CTG ATA CGA GCT TCA ACT CAC GTG CTG TTT CAT GGC TGT TAT TTT ATG GGA
Leu Ile Arg Ala Ser Thr His Val Leu Phe His Gly Cys Tyr Phe Met Gly
```

FIG. IG

```
      2430         2440         2450         2460         2470
ATT ATG GGC ACT TGT ATT GAG GTG GGG GCG GGA GCT TAC ATT CGG GGT TGT
Ile Met Gly Thr Cys Ile Glu Val Gly Ala Gly Ala Tyr Ile Arg Gly Cys

     2480         2490         2500         2510         2520
GAG TTT GTG GGC TGT TAC CGG GGA ATC TGT TCT ACT TCT AAC AGA GAT ATT
Glu Phe Val Gly Cys Tyr Arg Gly Ile Cys Ser Thr Ser Asn Arg Asp Ile

   2530         2540         2550         2560         2570
AAG GTG AGG CAG TGC AAC TTT GAC AAA TGC TTA CTG GGT ATT ACT TGT AAG
Lys Val Arg Gln Cys Asn Phe Asp Lys Cys Leu Leu Gly Ile Thr Cys Lys

  2580         2590         2600         2610         2620
GGG GAC TAT CGT CTT TCG GGA AAT GTG TGT TCT GAG ACT TTC TGC TTT GCT
Gly Asp Tyr Arg Leu Ser Gly Asn Val Cys Ser Glu Thr Phe Cys Phe Ala

 2630         2640         2650         2660         2670
CAT TTA GAG GGA GAG GGT TTG GTT AAA AAC AAC ACA GTC AAG TCC CCT AGT
His Leu Glu Gly Glu Gly Leu Val Lys Asn Asn Thr Val Lys Ser Pro Ser

2680         2690         2700         2710         2720
CGC TGG ACC AGC GAG TCT GGC TTT TCC ATG ATA ACT TGT GCA GAC GGC AGG
Arg Trp Thr Ser Glu Ser Gly Phe Ser Met Ile Thr Cys Ala Asp Gly Arg
```

FIG. 1H

```
2730          2740          2750          2760          2770
GTT ACG CCT TTG GGT TCC CTC CAC ATT GTG GGC AAC CGT TGT AGG CGT TGG
Val Thr Pro Leu Gly Ser Leu His Ile Val Gly Asn Arg Cys Arg Arg Trp

2780          2790          2800          2810          2820          2830
CCA ACC ATG CAG GGG AAT GTG TTT ATC ATG TCT AAA CTG TAT CTG GGC AAC
Pro Thr Met Gln Gly Asn Val Phe Ile Met Ser Lys Leu Tyr Leu Gly Asn

            2840          2850          2860          2870          2880
AGA ATA GGG ACT GTA GCC CTG CCC CAG TGT GCT TTC TAC AAG TCC AGC ATT
Arg Ile Gly Thr Val Ala Leu Pro Gln Cys Ala Phe Tyr Lys Ser Ser Ile

          2890          2900          2910          2920          2930
TGT TTG GAG GAG AGG GCG ACA AAC AAG CTG GTC TTG GCT TGT GCT TTT GAG
Cys Leu Glu Glu Arg Ala Thr Asn Lys Leu Val Leu Ala Cys Ala Phe Glu

        2940          2950          2960          2970          2980
AAT AAT GTA CTG GTG TAC AAA GTG CTG AGA CGG GAG AGT CCC TCA ACC GTG
Asn Asn Val Leu Val Tyr Lys Val Leu Arg Arg Glu Ser Pro Ser Thr Val

      2990          3000          3010          3020          3030
AAA ATG TGT GTT TGT GGG ACT TCT CAT TAT GCA AAG CCT TTG ACA CTG GCA
Lys Met Cys Val Cys Gly Thr Ser His Tyr Ala Lys Pro Leu Thr Leu Ala
```

FIG. 11

```
   3040          3050          3060          3070          3080
ATT ATT TCT TCA GAT ATT CGG GCT AAT CGA TAC ATG TAC ACT GTG GAC TCA
Ile Ile Ser Ser Asp Ile Arg Ala Asn Arg Tyr Met Tyr Thr Val Asp Ser

  3090          3100          3110       3120       3130       3140
ACA GAG TTC ACT TCT GAC GAG GAT T AAAAGTGGGC GGGGCCAAGA GGGGTATAAA
Thr Glu Phe Thr Ser Asp Glu Asp End

      3150       3160       3170       3180       3190       3200
TAGGTGGGGA GGTTGAGGGG AGCCGTAGTT TCTGTTTTTC CCAGACTGGG GGGGACAAC ATG
                                                                 Met

      3210          3220          3230          3240          3250
GCC GAG GAA GGG CGC ATT TAT GTG CCT TAT GTA ACT GCC CGC CTG CCC AAG
Ala Glu Glu Gly Arg Ile Tyr Val Pro Tyr Val Thr Ala Arg Leu Pro Lys

     3260          3270          3280          3290          3300
TGG TCG GGT TCG GTG CAG GAT AAG ACG GGC TCG AAC ATG TTG GGG GGT GTG
Trp Ser Gly Ser Val Gln Asp Lys Thr Gly Ser Asn Met Leu Gly Gly Val

   3310          3320          3330          3340          3350
GTA CTC CCT CCT AAT TCA CAG GCG CAC CGG ACG GAG ACC GTG GGC ACT GAG
Val Leu Pro Pro Asn Ser Gln Ala His Arg Thr Glu Thr Val Gly Thr Glu
```

FIG. IJ

```
  3360          3370          3380          3390          3400
GCC ACC AGA GAC AAC CTG CAC GCC GAG GGA GCG CGT CGT CCT GAG GAT CAG
Ala Thr Arg Asp Asn Leu His Ala Glu Gly Ala Arg Arg Pro Glu Asp Gln

  3410          3420          3430          3440          3450
ACG CCC TAC ATG ATC TTG GTG GAG GAC TCT CTG GGA GGT TTG AAG AGG CGA
Thr Pro Tyr Met Ile Leu Val Glu Asp Ser Leu Gly Gly Leu Lys Arg Arg

 3460          3470          3480          3490          3500
ATG GAC TTG CTG GAA GAA TCT AAT CAG CAG CTG CTG GCA ACT CTC AAC CGT
Met Asp Leu Leu Glu Glu Ser Asn Gln Gln Leu Leu Ala Thr Leu Asn Arg

 3510          3520          3530          3540          3550
CTC CGT ACA GGA CTC GCT GCC TAT GTG CAG GCT AAC CTT GTG GGC GGC CAA
Leu Arg Thr Gly Leu Ala Ala Tyr Val Gln Ala Asn Leu Val Gly Gly Gln

 3560          3570          3580          3590          3600          3610
GTT AAC CCC TTT GTT TAAATA AAAATACACT CATACAGTTT ATTATGCTGT
Val Asn Pro Phe Val End

       3620          3630          3640          3650          3660          3670
CAATAAAATT CTTTATTTTT CCTGTGATAA TACCGTGTCC AGCGTGCTCT GTCAATAAGG

       3680          3690          3700          3710          3720          3730
GTCCTATGCA TCCTGAGAAG GGCCTCATAT ACCCATGGCA TGAATATTAA GATACATGGG
```

FIG. 1K

```
3740      3750      3760      3770      3780      3790
CATAAGGCCC TCAGAAGGGT TGAGGTAGAG CCACTGCAGA CTTTCGTGGG GAGGTAAGGT

3800      3810      3820      3830      3840      3850
GTTGTAAATA ATCCAGTCAT ACTGACTGTG CTGGGCGTGG AAGGAAAAGA TGTCTTTTAG

3860      3870      3880      3890      3900      3910
AAGAAGGGTG ATTGGCAAAG GGAGGCTCTT AGTGTAGGTA TTGATAAATC TGTTCAGTTG

3920      3930      3940      3950      3960      3970
GGAGGGATGC ATTCGGGGGC TAATAAGGTG GAGTTTAGCC TGAATCTTAA GGTTGGCAAT

3980      3990      4000      4010      4020      4030
GTTGCCCCCT AGGTCTTTGC GAGGATTCAT GTTGTGCAGT ACCACAAAAA CAGAGTAGCC

4040      4050      4060
TGTGCATTTG GGGAATTTAT CATGAAGCT T
```

FIG. IL

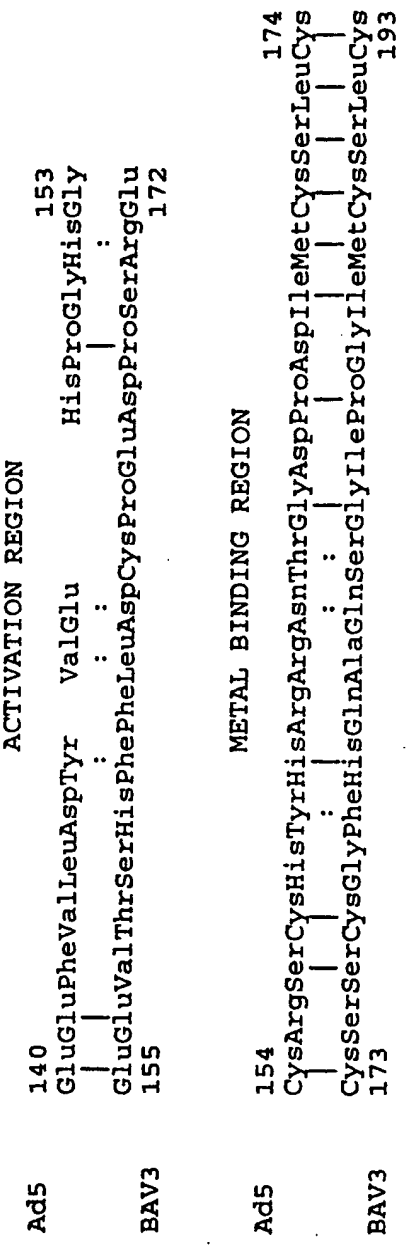

ACTIVATION REGION
Ad5 140 153
GluGluPheValLeuAspTyr ValGlu HisProGlyHisGly
BAV3 155 172
METAL BINDING REGION
Ad5 154 174
CysArgSerCysHisTyrHisArgArgAsnThrGlyAspProAspIleMetCysSerLeuCys
BAV3 173 193
PROMOTER BINDING REGION
Ad5 175 189
TyrMetArgThrCys GlyMetPheValTyrSerProValSerGluProGluProGlu
BAV3 194 208

FIG. 2A

```
                                        Rb BINDING SEQUENCE
Ad5     120                                          132
        IleAspLeuThrCysHisGluAlaGlyPheProProSer
         :   |  |      |  |  |           |  |  |
        ValAspLeuGluCysHisGluVal    LeuProProSer
BAV3    26                                           37
```

FIG. 2B

```
Ad5     82                                                                  100
        LeuAspPheSerThrProGlyArgAlaAlaAlaAlaValAlaPheLeuSerPheIle
         |  |         |  |  |  |         |  |     |     |     |  |
        LeuAsp      ThrProGlyArgValValAlaAlaLeuAlaLeuLeuValPheIle
BAV3     83                                                                  99
```

FIG. 3A

```
Ad5     20                  26
        GlnSerSerAsnSerThrSer
         |  |  |     |  |  |
        GlnSerSerArgSerThrSer
BAV3    136                 142
```

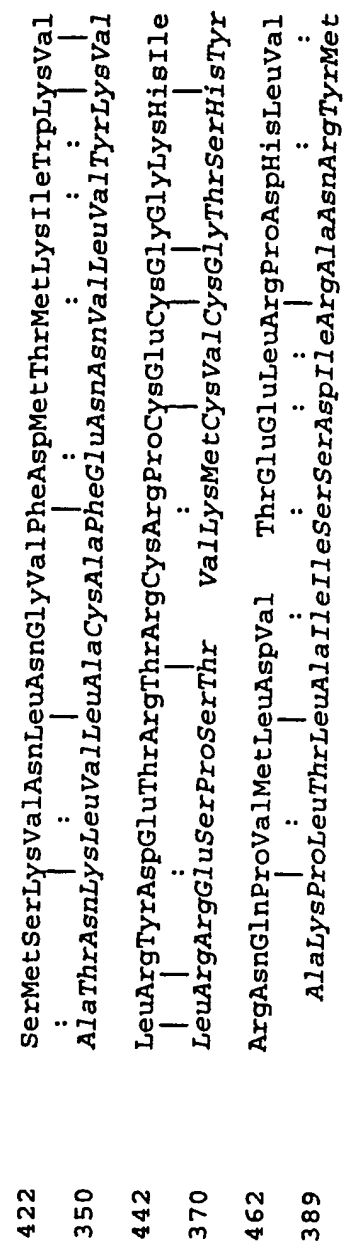
FIG. 3B

```
Ad5   150   GlnLysTyrSerIleGluGlnLeuThrThrTyrTrpLeuGlnProGlyAspAspPheGlu
                :  |        |     :     :  |           |     |        |
BAV3   74   GluArgTyrLysPheGluAspIleLysSerTyrGluAlaLeuProGluAspAsnLeuGlu

170         GluAlaIleArgValTyrAlaLysValAlaLeuArgProAspCysLysTyrLysIleSer
                   |     :     |  |  :     |     |           |     :  :
94          GlnLeuIleAlaMetHisAlaLysIleLysLeuLeuProGlyArgGluTyrGluLeuThr

190         LysLeuValAsnIleArgAsnCysCysTyrIleSerGlyAsnGlyAlaGluValGluIle
                   :  |  |        |     |  :     |  |  |  |     :     :
114         GlnProLeuAsnIleThrSerCysAlaTyrValLeuGlyAsnGlyAlaThrIleArgVal

210         AspThrGluAspArgValAlaPheArgCysSerMetIleAsnMetTrpProGlyValLeu
                   |           |     |           :     :     |     |
134         ThrGlyGluAlaSerProAlaIleArgValGlyAlaMetAlaValGlyProCysValThr

230         GlyMetAspGlyValValIleMetAsnValArgPheThr   GlyProAsnPheSerGly
             |  |     |  |        :  |     |  |                       |
154         GlyMetThrGlyValThrPheValAsnCysArgPheGluArgGluSerThrIleArgGly

249         ThrValPheLeuAlaAsnThrAsnLeuIleLeuHisGlyValSerPheTyr   GlyPhe
             :  :        |     |     :  :     |  |        :  :     |
174         SerLeuIleArgAlaSerThrHisValLeuPheHisGlyCys   TyrPheMetGlyIle

268         AsnAsnThrCysValGluAlaTrpThrAspValArgValArgGlyCysAlaPheTyrCys
                   |  |  :  |        :           :  |  |  |     |
193         MetGlyThrCysIleGluValGlyAlaGlyAlaTyrIleArgGlyCysGluPheValGly
```

FIG. 4A

```
288    CysTrpLysGlyValValCysArgProLysSerArgAla   SerIleLysLysCysLeu
        |  :  :  |  :     |              |           :  :     |
213    CysTyrArgGlyIle   CysSerThrSerAsnArgAspIleLysValArgGlnCysAsn

307    PheGluArgCysThrLeuGlyIleLeuSerGluGlyAsnSerArgValArgHisAsnVal
        |  :  :  |     |  |  |           |        |  :        |  |
232    PheAspLysCysLeuLeuGlyIleThrCysLysGlyAspTyrArgLeuSerGlyAsnVal

327    AlaSerAspCysGlyCysPheMetLeuValLysSerValAlaValIleLysHisAsnMet
           |  :        |  |        :              :  :  |     |
252    CysSerGluThrPheCysPheAlaHisLeuGluGlyGluGlyLeuValLysAsnAsnThr

347    Val   CysGlyAsn         CysGluAspArgAlaSerGlnMetLeuThrCysSerAsp
        |                          :              |  :  |  |  :  |
272    ValLysSerProSerArgTrpThrSerGluSerGlyPheSerMetIleThrCysAlaAsp

364    GlyAsnCysHisLeuLeuLysThrIleHisVal   AlaSerHisSerArgLysAlaTrp
        |              |     :  :  |  :           :     |  :     |
292    GlyArgValThrProLeuGlySerLeuHisIleValGlyAsnArgCysArgArg   Trp

383    ProValPheGluHisAsnIleLeuThrArgCysSerLeuHisLeuGlyAsnArgArgGly
        |              |  :                 |     |  |  |  |     |
311    ProThrMetGlnGlyAsnValPheIleMetSerLysLeuTyrLeuGlyAsnArgIleGly

403       ValPheLeuProTyrGlnCysAsnLeuSerHisThrLysIleLeuLeuGluProGlu
           |     |  |     |  |           :  :     |     |  |
331    ThrValAlaLeuPro   GlnCysAlaPheTyrLysSerSerIleCysLeuGluGluArg
```

FIG. 4B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350 AlaThrAsnLysLeuValLeuAlaCysAlaPheGluAsnAsnValLeuValTyrLysVal
442 LeuArgTyrAspGluThrArgThrArgCysArgProCysGluCysGlyGlyLysHisIle
370 LeuArgArgGluSerProSerThr ValLysMetCysValCysGlyThrSerHisTyr
462 ArgAsnGlnProValMetLeuAspVal ThrGluGluLeuArgProAspHisLeuVal
389 AlaLysProLeuThrLeuAlaIleIleSerSerAspIleArgAlaAsnArgTyrMet
481 LeuAlaCysThrArgAlaGluPheGlySerSerAspGluAspThrAspEnd
408 TyrThrValAspSerThrGluPhe ThrSerAspGluAspEnd

FIG. 4C

```
Ad5     1   MetSerThrAsnSerPheAspGlySerIleValSerSerTyrLeuThrThrArgMetPro
BAV3    1   MetAla   Glu      GluGlyArgIleTyrValProTyrValThrAlaArgLeuPro
           21   ProTrpAlaGlyValArgGlnAsnValMetGlySerSerIleAspGlyArgProValLeu
           18   LysTrpSerGlySerValGlnAspLysThrGlySerAsnMetLeuGlyGlyValValLeu
           41   ProAlaAsnSerThrThrLeuThrTyrGluThrValSerGlyThrProLeuGluThrAla
           38   ProProAsnSerGlnAlaHisArgThrGluThrVal   GlyThrGlu   AlaThr
           61   AlaSerAlaAlaAlaSerAlaAlaAlaAlaThrAlaArgGlyIleValThrAspPheAla
           55      ArgAspAsnLeuHisAlaGluGlyAlaArg   ArgProGluAspGlnThr   Pro
           81   PheLeuSerProLeuAlaSerSerAlaAlaSerArgSerSerAlaArgAspAspLysLeu
           72   TyrMetIle   LeuValGluAspSerLeuGlyGlyLeuLysArgArgMetAspLeuLeu
          101   ThrAlaLeuLeuAlaGlnLeu   AspSerLeuThrArgGluLeuAsnValValSerGln
           91   GluGluSerAsnGlnGlnLeuLeuAlaThrLeuAsnArg   LeuArgThr   Gly
          120   GlnLeuLeuAspLeuArgGlnGlnValSerAlaLeuLysAlaSerSerProProAsnAla
          108      LeuAlaAlaTyr   ValGln   AlaAsnLeuValGlyGlyGlnValAsnProPhe
          140   ValEnd
          125   ValEnd
```

FIG. 5

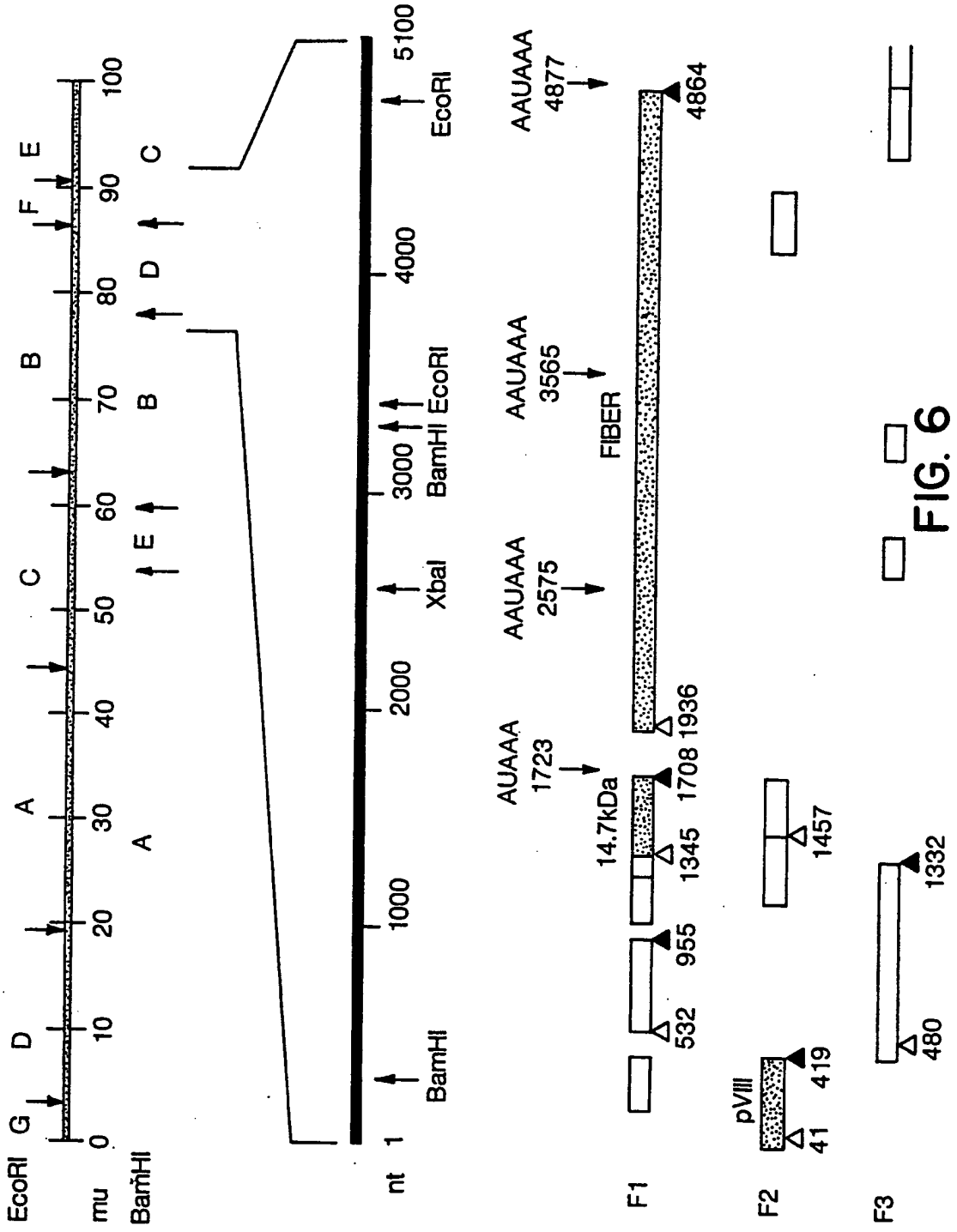

EcoRI
G
D
A
C
E
F
E
B
D
C
mu
BamHI
0
10
20
30
40
50
60
70
80
90
100
A
E
B
A
nt
1
1000
2000
3000
4000
5100
BamHI
XbaI
BamHI
EcoRI
EcoRI
AUAAA
1723
AAUAAA
2575
AAUAAA
3565
FIBER
AAUAAA
4877
14.7kDa
F1
532
955
1345
1708
1936
4864
pVIII
F2
41
419
1457
F3
480
1332

FIG. 6

```
                10                  20                  30                  40                  50
    C CTC ATC AAA CAA CCC GTG GTG GGC ACC ACC CAC GTG GAA ATG CCT CGC AAC
ORF 1 Leu Ile Lys Gln Pro Val Val Gly Thr Thr His Val Glu Met Pro Arg Asn

          60                  70                  80                  90                  100
    GAA GTC CTA GAA CAA CAT CTG ACC TCA CAT GGC GCT CAA ATC GCG GGC GGA
    Glu Val Leu Glu Gln His Leu Thr Ser His Gly Ala Gln Ile Ala Gly Gly

       110                 120                 130                 140                 150
    GGC GCT GCG GGC GAT TAC TTT AAA AGC CCC ACT TCA GCT CGA ACC CTT ATC
    Gly Ala Ala Gly Asp Tyr Phe Lys Ser Pro Thr Ser Ala Arg Thr Leu Ile

    160                 170                 180                 190                 200
    CCG CTC ACC GCC TCC TGC TTA AGA CCA GAT GGA GTC TTT CAA CTA GGA GGA
    Pro Leu Thr Ala Ser Cys Leu Arg Pro Asp Gly Val Phe Gln Leu Gly Gly

   210                 220                 230                 240                 250
    GGC TCG CGT TCA TCT TTC AAC CCC CTG CAA ACA GAT TTT GCC TTC CAC GCC
    Gly Ser Arg Ser Ser Phe Asn Pro Leu Gln Thr Asp Phe Ala Phe His Ala

  260                 270                 280                 290                 300
    CTG CCC TCC AGA CCG CGC CAC GGG GGC ATA GGA TCC AGG CAG TTT GTA GAG
    Leu Pro Ser Arg Pro Arg His Gly Gly Ile Gly Ser Arg Gln Phe Val Glu
```

FIG. 7A

```
310          320          330          340          350
GAA TTT GTG CCC GCC GTC TAC CTC AAC CCC TAC TCG GGA CCG CCG GAC TCT
Glu Phe Val Pro Ala Val Tyr Leu Asn Pro Tyr Ser Gly Pro Pro Asp Ser

360          370          380          390          400
TAT CCG GAC CAG TTT ATA CGC CAC TAC AAC GTG TAC AGC AAC TCT GTG AGC
Tyr Pro Asp Gln Phe Ile Arg His Tyr Asn Val Tyr Ser Asn Ser Val Ser
                                                   ORF 2  Ala
410          420          430          440          450          460
GGT TAT AGC T GAG ATT GTA AGA CTC TCC TAT CTG TCT CTG TGC TGC TTT TCC
Gly Tyr Ser
 Val Ile Ala  Glu Ile Val Arg Leu Ser Tyr Leu Ser Leu Cys Cys Phe Ser

         470          480          490          500          510
GCT TCA AGC CCC ACA AGC ATG AAG GGG TTT CTG CTC ATC TTC AGC CTG CTT
Ala Ser Ser Pro Thr Ser Met Lys Gly Phe Leu Leu Ile Phe Ser Leu Leu

       520          530          540          550          560
GTG CAT TGT CCC CTA ATT CAT GTT GGG ACC ATT AGC TTC TAT GCT GCA AGG
                ORF 3  Phe Met Leu Gly Pro Leu Ala Ser Met Leu Gln Gly
Val His Cys Pro Leu Ile His Val Gly Thr Ile Ser Phe Tyr Ala Ala Arg
```

FIG. 7B

570 580 590 600 610
CCC GGG TCT GAG CCT AAC GCG ACT TAT GTT TGT GAC TAT GGA AGC GAG TCA
Pro Gly Leu Ser Leu Thr Arg Leu Met Phe Val Thr Met Glu Ala Ser Gln
Pro Gly Ser Glu Pro Asn Ala Thr Tyr Val Cys Asp Tyr Gly Ser Glu Ser

620 630 640 650 660
GAT TAC AAC CCC ACC ACG GTT CTG TGG TTG GCT CGA GAG ACC GAT GGC TCC
Ile Thr Thr Pro Pro Arg Phe Cys Gly Trp Leu Glu Arg Pro Met Ala Pro
Asp Tyr Asn Pro Thr Thr Val Leu Trp Leu Ala Arg Glu Thr Asp Gly Ser

670 680 690 700 710
TGG ATC TCT GTT CTT TTC CGT CAC AAC GGC TCC TCA ACT GCA GCC CCC GGG
Gly Ser Leu Phe Phe Ser Val Thr Thr Ala Pro Gln Leu Gln Pro Pro Gly
Trp Ile Ser Val Leu Phe Arg His Asn Gly Ser Ser Thr Ala Ala Pro Gly

720 730 740 750 760
GTC GTC GCG CAC TTT ACT GAC CAC AAC AGC AGC ATT GTG GTG CCC CAG TAT
Ser Ser Arg Thr Leu Leu Thr Thr Thr Ala Ala Leu Trp Cys Pro Ser Ile
Val Val Ala His Phe Thr Asp His Asn Ser Ser Ile Val Val Pro Gln Tyr

770 780 790 800 810
TAC CTC CTC AAC AAC TCA CTC TCT AAG CTC TGC TGC TCA TAC CGG CAC AAC
Thr Ser Ser Thr Thr His Ser Leu Ser Ser Ala Ala His Thr Gly Thr Thr
Tyr Leu Leu Asn Asn Ser Leu Ser Lys Leu Cys Cys Ser Tyr Arg His Asn

FIG. 7C

820 830 840 850 860
GAG CGT TCT CAG TTT ACC TGC AAA CAA GCT GAC GTC CCT ACC TGT CAC GAG
Ser Val Leu Ser Leu Pro Ala Asn Lys Leu Thr Ser Leu Pro Val Thr Ser
Glu Arg Ser Gln Phe Thr Cys Lys Gln Ala Asp Val Pro Thr Cys His Glu

870 880 890 900 910 920
CCC GGC AAG CCG CTC ACC CTC CGC GTC TCC CCC GCG CTG GGA ACT GCC CAC
Pro Ala Ser Arg Ser Pro Ser Ala Ser Pro Pro Arg Trp Glu Leu Pro Thr
Pro Gly Lys Pro Leu Thr Leu Arg Val Ser Pro Ala Leu Gly Thr Ala His

930 940 950 960 970
CAA GCA GTC ACT TGG TTT TTT CAA AAT GTA CCC ATA GCT ACT GTT TAC CGA
Lys Gln Ser Leu Gly Phe Phe Lys Met Tyr Pro
Gln Ala Val Thr Trp Phe Phe Gln Asn Val Pro Ile Ala Thr Val Tyr Arg

980 990 1000 1010 1020
CCT TGG GGC AAT GTA ACT TGG TTT TGT CCT CCC TTC ATG TGT ACC TTT AAT
Pro Trp Gly Asn Val Thr Trp Phe Cys Pro Pro Phe Met Cys Thr Phe Asn

1030 1040 1050 1060 1070
GTC AGC CTG AAC TCC CTA CTT ATT TAC AAC TTT TCT GAC AAA ACC GGG GGG
Val Ser Leu Asn Ser Leu Leu Ile Tyr Asn Phe Ser Asp Lys Thr Gly Gly

FIG. 7D

```
   1080          1090           1100          1110          1120
CAA TAC ACA GCT CTC ATG CAC TCC GGA CCT GCT TCC CTC TTT CAG CTC TTT
Gln Tyr Thr Ala Leu Met His Ser Gly Pro Ala Ser Leu Phe Gln Leu Phe

  1130          1140           1150          1160          1170
AAG CCA ACG ACT TGT GTC ACC AAG GTG GAG GAC CCG CCG TAT GCC AAC GAC
Lys Pro Thr Thr Cys Val Thr Lys Val Glu Asp Pro Pro Tyr Ala Asn Asp

 1180          1190           1200          1210          1220
CCG GCC TCG CCT GTG TGG CGC CCA CTG CTT TTT GCC TTC GTC CTC TGC ACC
Pro Ala Ser Pro Val Trp Arg Pro Leu Leu Phe Ala Phe Val Leu Cys Thr

 1230          1240           1250          1260          1270
GGC TGC GCG GTG TTG TTA ACC GCC TTC GGT CCA TCG ATT CTA TCC GGT ACC
                    ORF 4  Pro Pro Ser Val His Arg Phe Tyr Pro Val Pro
Gly Cys Ala Val Leu Leu Thr Ala Phe Gly Pro Ser Ile Leu Ser Gly Thr

1280          1290           1300          1310          1320
CGA AAG CTT ATC TCA GCC CGC TTT TGG AGT CCC GAG CCC TAT ACC ACC CTC
 Glu Ser Leu Ser Gln Pro Ala Phe Gly Val Pro Ser Pro Ile Pro Pro Ser
Arg Lys Leu Ile Ser Ala Arg Phe Trp Ser Pro Glu Pro Tyr Thr Thr Leu
```

FIG. 7E

```
1330          1340          1350          1360          1370          1380
CAC T AAC AGT CCC CCC ATG GAG CCA GAC GGA GTT CAT GCC GAG CAG CAG TTT
 Thr  Asn Ser Pro Pro Met Glu Pro Asp Gly Val His Ala Glu Gln Gln Phe
His

          1390          1400          1410          1420          1430
ATC CTC AAT CAG ATT TCC TGC GCC AAC ACT GCC CTC CAG CGT CAA AGG GAG
Ile Leu Asn Gln Ile Ser Cys Ala Asn Thr Ala Leu Gln Arg Gln Arg Glu

       1440          1450          1460          1470          1480
GAA CTA GCT TCC CTT GTC ATG TTG CAT GCC TGT AAG CGT GGC CTC TTT TGT
Glu Leu Ala Ser Leu Val Met Leu His Ala Cys Lys Arg Gly Leu Phe Cys
 ORF 5  Leu Pro Leu Ser Cys Cys Met Pro Val Ser Val Ala Ser Phe Val

      1490          1500          1510          1520          1530
CCA GTC AAA ACT TAC AAG CTC AGC CTC AAC GCC TCG GCC AGC GAG CAC AGC
Pro Val Lys Thr Tyr Lys Leu Ser Leu Asn Ala Ser Ala Ser Glu His Ser
 Gln Ser Lys Leu Thr Ser Ser Ala Ser Thr Pro Arg Pro Ala Ser Thr Ala

     1540          1550          1560          1570          1580
CTG CAC TTT GAA AAA AGT CCC TCC CGA TTC ACC CTG GTC AAC ACT CAC GCC
Leu His Phe Glu Lys Ser Pro Ser Arg Phe Thr Leu Val Asn Thr His Ala
 Cys Thr Leu Lys Lys Val Pro Pro Asp Ser Pro Trp Ser Thr Leu Thr Pro
```

FIG. 7F

```
   1590          1600          1610          1620          1630
GGA GCT TCT GTG CGA GTG GCC CTA CAC CAC CAG GGA GCT TCC GGC AGC ATC
Gly Ala Ser Val Arg Val Ala Leu His His Gln Gly Ala Ser Gly Ser Ile
 Glu Leu Leu Cys Glu Trp Pro Tyr Thr Thr Arg Glu Leu Pro Ala Ala Ser

  1640          1650          1660          1670          1680
CGC TGT TCC TGT TCC CAC GCC GAG TGC CTC CCC GTC CTC CTC AAG ACC CTC
Arg Cys Ser Cys Ser His Ala Glu Cys Leu Pro Val Leu Leu Lys Thr Leu
 Ala Val Pro Val Pro Thr Pro Ser Ala Ser Pro Ser Ser Ser Arg Pro Ser

 1690          1700          1710          1720          1730          1740
TGT GCC TTT AAC TTT TTA GAT TAG CTGAAAGCAA ATATAAAATG GTGTGCTTAC
Cys Ala Phe Asn Phe Leu Asp
 Val Pro Leu Thr Phe

      1750          1760          1770          1780          1790
CGTAATTCTG TTTTGACTTG TGTGCTTGA TTT CTC CCC CTG CGC CGT AAT CCA GTG

 1800          1810          1820          1830          1840
CCC CTC TTC AAA ACT CTC GTA CCC TAT GCG ATT CGC ATA GGC ATA TTT TCT

1850          1860          1870          1880          1890
 AAA AGC TCT GAA GTC AAC ATC ACT CTC AAA CAC TTC TCC GTT GTA GGT TAC
```

FIG. 7G

```
1900          1910          1920          1930          1940          1950
TTT CAT CTA CAG ATA AAG TCA TCC ACC GGT T AAC ATC ATG AAG AGA AGT GTG
          ORF 6  Ser His Pro Pro Val  Asn Ile Met Lys Arg Ser Val

          1960          1970          1980          1990          2000
CCC CAG GAC TTT AAT CTT GTG TAT CCG TAC AAG GCT AAG AGG CCC AAC ATC
Pro Gln Asp Phe Asn Leu Val Tyr Pro Tyr Lys Ala Lys Arg Pro Asn Ile

          2010          2020          2030          2040          2050
ATG CCG CCC TTT TTT GAC CGC AAT GGC TTT GTT GAA AAC CAA GAA GCC ACG
Met Pro Pro Phe Phe Asp Arg Asn Gly Phe Val Glu Asn Gln Glu Ala Thr

          2060          2070          2080          2090          2100
CTA GCC ATG CTT GTG GAA AAG CCG CTC ACG TTC GAC AAG GAA GGT GCG CTG
Leu Ala Met Leu Val Glu Lys Pro Leu Thr Phe Asp Lys Glu Gly Ala Leu

          2110          2120          2130          2140          2150
ACC CTG GGC GTC GGA CGC GGC ATC CGC ATT AAC CCC GCG GGG CTT CTG GAG
Thr Leu Gly Val Gly Arg Gly Ile Arg Ile Asn Pro Ala Gly Leu Leu Glu

          2160          2170          2180          2190          2200
ACA AAC GAC CTC GCG TCC GCT GTC TTC CCA CCG CTG GCC TCC GAT GAG GCC
Thr Asn Asp Leu Ala Ser Ala Val Phe Pro Pro Leu Ala Ser Asp Glu Ala
```

FIG. 7H

```
  2210          2220          2230          2240          2250
GGC AAC GTC ACG CTC AAC ATG TCT GAC GGG CTA TAT ACT AAG GAC AAC AAG
Gly Asn Val Thr Leu Asn Met Ser Asp Gly Leu Tyr Thr Lys Asp Asn Lys

 2260          2270          2280          2290          2300
CTA GCT GTC AAA GTA GGT CCC GGG CTG TCC CTC GAC TCC AAT AAT GCT CTC
Leu Ala Val Lys Val Gly Pro Gly Leu Ser Leu Asp Ser Asn Asn Ala Leu

2310          2320          2330          2340          2350
CAG GTC CAC ACA GGC GAC GGG CTC ACG GTA ACC GAT GAC AAG GTG TCT CTA
Gln Val His Thr Gly Asp Gly Leu Thr Val Thr Asp Asp Lys Val Ser Leu

2360          2370          2380          2390          2400
AAT ACC CAA GCT CCC CTC TCG ACC ACC AGC GCG GGC CTC TCC CTA CTT CTG
Asn Thr Gln Ala Pro Leu Ser Thr Thr Ser Ala Gly Leu Ser Leu Leu Leu

2410          2420          2430          2440          2450          2460
GGT CCC AGC CTC CAC TTA GGT GAG GAG GAA CGA CTA ACA GTA AAC ACC GGA
Gly Pro Ser Leu His Leu Gly Glu Glu Glu Arg Leu Thr Val Asn Thr Gly

          2470          2480          2490          2500          2510
GCG GGC CTC CAA ATT AGC AAT AAC GCT CTG GCC GTA AAA GTA GGT TCA GGT
Ala Gly Leu Gln Ile Ser Asn Asn Ala Leu Ala Val Lys Val Gly Ser Gly
```

FIG. 7I

```
      2520          2530          2540          2550          2560
ATC ACC GTA GAT GCT CAA AAC CAG CTC GCT GCA TCC CTG GGG GAC GGT CTA
Ile Thr Val Asp Ala Gln Asn Gln Leu Ala Ala Ser Leu Gly Asp Gly Leu

      2570          2580          2590          2600          2610
GAA AGC AGA GAT AAT AAA ACT GTC GTT AAG GCT GGG CCC GGA CTT ACA ATA
Glu Ser Arg Asp Asn Lys Thr Val Val Lys Ala Gly Pro Gly Leu Thr Ile

      2620          2630          2640          2650          2660
ACT AAT CAA GCT CTT ACT GTT GCT ACC GGG AAC GGC CTT CAG GTC AAC CCG
Thr Asn Gln Ala Leu Thr Val Ala Thr Gly Asn Gly Leu Gln Val Asn Pro

      2670          2680          2690          2700          2710
GAA GGG CAA CTG CAG CTA AAC ATT ACT GCC GGT CAG GGC CTC AAC TTT GCA
Glu Gly Gln Leu Gln Leu Asn Ile Thr Ala Gly Gln Gly Leu Asn Phe Ala

      2720          2730          2740          2750          2760
AAC AAC AGC CTC GCC GTG GAG CTG GGC TCG GGC CTG CAT TTT CCC CCT GGC
Asn Asn Ser Leu Ala Val Glu Leu Gly Ser Gly Leu His Phe Pro Pro Gly

      2770          2780          2790          2800          2810
CAA AAC CAA GTA AGC CTT TAT CCC GGA GAT GGA ATA GAC ATC CGA GAT AAT
Gln Asn Gln Val Ser Leu Tyr Pro Gly Asp Gly Ile Asp Ile Arg Asp Asn
```

FIG. 7J

```
2820          2830          2840          2850          2860
AGG GTG ACT GTG CCC GCT GGG CCA GGC CTG AGA ATG CTC AAC CAC CAA CTT
Arg Val Thr Val Pro Ala Gly Pro Gly Leu Arg Met Leu Asn His Gln Leu

2870          2880          2890          2900          2910
GCC GTA GCT TCC GGA GAC GGT TTA GAA GTC CAC AGC GAC ACC CTC CGG TTA
Ala Val Ala Ser Gly Asp Gly Leu Glu Val His Ser Asp Thr Leu Arg Leu

2920          2930          2940          2950          2960          2970
AAG CTC TCC CAC GGC CTG ACA TTT GAA AAT GGC GCC GTA CGA GCA AAA CTA
Lys Leu Ser His Gly Leu Thr Phe Glu Asn Gly Ala Val Arg Ala Lys Leu

              2980          2990          3000          3010          3020
GGA CCA GGA CTT GGC ACA GAC GAC TCT GGT CGG TCC GTG GTT CGC ACA GGT
Gly Pro Gly Leu Gly Thr Asp Asp Ser Gly Arg Ser Val Val Arg Thr Gly

         3030          3040          3050          3060          3070
CGA GGA CTT AGA GTT GCA AAC GGC CAA GTC CAG ATC TTC AGC GGA AGA GGC
Arg Gly Leu Arg Val Ala Asn Gly Gln Val Gln Ile Phe Ser Gly Arg Gly

         3080          3090          3100          3110          3120
ACC GCC ATC GGC ACT GAT AGC AGC CTC ACT CTC AAC ATC CGG GCG CCC CTA
Thr Ala Ile Gly Thr Asp Ser Ser Leu Thr Leu Asn Ile Arg Ala Pro Leu
```

FIG. 7K

```
     3130          3140          3150          3160          3170
CAA TTT TCT GGA CCC GCC TTG ACT GCT AGT TTG CAA GGC AGT GGT CCG ATT
Gln Phe Ser Gly Pro Ala Leu Thr Ala Ser Leu Gln Gly Ser Gly Pro Ile

   3180          3190          3200          3210          3220
ACT TAC AAC AGC AAC AAT GGC ACT TTC GGT CTC TCT ATA GGC CCC GGA ATG
Thr Tyr Asn Ser Asn Asn Gly Thr Phe Gly Leu Ser Ile Gly Pro Gly Met

  3230          3240          3250          3260          3270
TGG GTA GAC CAA AAC AGA CTT CAG GTA AAC CCA GGC GCT GGT TTA GTC TTC
Trp Val Asp Gln Asn Arg Leu Gln Val Asn Pro Gly Ala Gly Leu Val Phe

 3280          3290          3300          3310          3320
CAA GGA AAC AAC CTT GTC CCA AAC CTT GCG GAT CCG CTG GCT ATT TCC GAC
Gln Gly Asn Asn Leu Val Pro Asn Leu Ala Asp Pro Leu Ala Ile Ser Asp

3330          3340          3350          3360          3370
AGC AAA ATT AGT CTC AGT CTC GGT CCC GGC CTG ACC CAA GCT TCC AAC GCC
Ser Lys Ile Ser Leu Ser Leu Gly Pro Gly Leu Thr Gln Ala Ser Asn Ala

3380          3390          3400          3410          3420
CTG ACT TTA AGT TTA GGA AAC GGG CTT GAA TTC TCC AAT CAA GCC GTT GCT
Leu Thr Leu Ser Leu Gly Asn Gly Leu Glu Phe Ser Asn Gln Ala Val Ala
```

FIG. 7L

```
3430          3440          3450          3460          3470          3480
   ATA AAA GCG GGC CGG GGC TTA CGC TTT GAG TCT TCC TCA CAA GCT TTA GAG
   Ile Lys Ala Gly Arg Gly Leu Arg Phe Glu Ser Ser Ser Gln Ala Leu Glu

             3490          3500          3510          3520          3530
   AGC AGC CTC ACA GTC GGA AAT GGC TTA ACG CTT ACC GAT ACT GTG ATC CGC
   Ser Ser Leu Thr Val Gly Asn Gly Leu Thr Leu Thr Asp Thr Val Ile Arg

          3540          3550          3560          3570          3580
   CCC AAC CTA GGG GAC GGC CTA GAG GTC AGA GAC AAT AAA ATC ATT GTT AAG
   Pro Asn Leu Gly Asp Gly Leu Glu Val Arg Asp Asn Lys Ile Ile Val Lys

          3590          3600          3610          3620          3630
   CTG GGC GCG AAT CTT CGT TTT GAA AAC GGA GCC GTA ACC GCC GGC ACC GTT
   Leu Gly Ala Asn Leu Arg Phe Glu Asn Gly Ala Val Thr Ala Gly Thr Val

       3640          3650          3660          3670          3680
   AAC CCT TCT GCG CCC GAG GCA CCA CCA ACT CTC ACT GCA GAA CCA CCC CTC
   Asn Pro Ser Ala Pro Glu Ala Pro Pro Thr Leu Thr Ala Glu Pro Pro Leu

      3690          3700          3710          3720          3730
   CGA GCC TCC AAC TCC CAT CTT CAA CTG TCC CTA TCG GAG GGC TTG GTT GTG
   Arg Ala Ser Asn Ser His Leu Gln Leu Ser Leu Ser Glu Gly Leu Val Val
```

FIG. 7M

```
  3740         3750         3760         3770         3780
CAT AAC AAC GCC CTT GCT CTC CAA CTG GGA GAC GGC ATG GAA GTA AAT CAG
His Asn Asn Ala Leu Ala Leu Gln Leu Gly Asp Gly Met Glu Val Asn Gln

  3790         3800         3810         3820         3830
CAC GGA CTT ACT TTA AGA GTA GGC TCG GGT TTG CAA ATG CGT GAC GGC ATT
His Gly Leu Thr Leu Arg Val Gly Ser Gly Leu Gln Met Arg Asp Gly Ile

3840         3850         3860         3870         3880
TTA ACA GTT ACA CCC AGC GGC ACT CCT ATT GAG CCC AGA CTG ACT GCC CCA
Leu Thr Val Thr Pro Ser Gly Thr Pro Ile Glu Pro Arg Leu Thr Ala Pro

3890         3900         3910         3920         3930
CTG ACT CAG ACA GAG AAT GGA ATC GGG CTC GCT CTC GGC GCC GGC TTG GAA
Leu Thr Gln Thr Glu Asn Gly Ile Gly Leu Ala Leu Gly Ala Gly Leu Glu

3940         3950         3960         3970         3980         3990
TTA GAC GAG AGC GCG CTC CAA GTA AAA GTT GGG CCC GGC ATG CGC CTG AAC
Leu Asp Glu Ser Ala Leu Gln Val Lys Val Gly Pro Gly Met Arg Leu Asn

         4000         4010         4020         4030         4040
CCT GTA GAA AAG TAT GTA ACC CTG CTC CTG GGT CCT GGC CTT AGT TTT GGG
Pro Val Glu Lys Tyr Val Thr Leu Leu Leu Gly Pro Gly Leu Ser Phe Gly
```

FIG. 7N

```
      4050          4060          4070          4080          4090
CAG CCG GCC AAC AGG ACA AAT TAT GAT GTG CGC GTT TCT GTG GAG CCC CCC
Gln Pro Ala Asn Arg Thr Asn Tyr Asp Val Arg Val Ser Val Glu Pro Pro

      4100          4110          4120          4130          4140
ATG GTT TTC GGA CAG CGT GGT CAG CTC ACA TTT TTA GTG GGT CAC GGA CTA
Met Val Phe Gly Gln Arg Gly Gln Leu Thr Phe Leu Val Gly His Gly Leu

      4150          4160          4170          4180          4190
CAC ATT CAA AAT TCC AAA CTT CAG CTC AAT TTG GGA CAA GGC CTC AGA ACT
His Ile Gln Asn Ser Lys Leu Gln Leu Asn Leu Gly Gln Gly Leu Arg Thr

      4200          4210          4220          4230          4240
GAC CCC GTC ACC AAC CAG CTG GAA GTG CCC CTC GGT CAA GGT TTG GAA ATT
Asp Pro Val Thr Asn Gln Leu Glu Val Pro Leu Gly Gln Gly Leu Glu Ile

      4250          4260          4270          4280          4290
GCA GAC GAA TCC CAG GTT AGG GTT AAA TTG GGC GAT GGC CTG CAG TTT GAT
Ala Asp Glu Ser Gln Val Arg Val Lys Leu Gly Asp Gly Leu Gln Phe Asp

      4300          4310          4320          4330          4340
TCA CAA GCT CGC ATC ACT ACC GCT CCT AAC ATG GTC ACT GAA ACT CTG TGG
Ser Gln Ala Arg Ile Thr Thr Ala Pro Asn Met Val Thr Glu Thr Leu Trp
```

FIG. 70

```
4350          4360          4370          4380          4390
ACC GGA ACA GGC AGT AAT GCT AAT GTT ACA TGG CGG GGC TAC ACT GCC CCC
Thr Gly Thr Gly Ser Asn Ala Asn Val Thr Trp Arg Gly Tyr Thr Ala Pro

4400          4410          4420          4430          4440
GGC AGC AAA CTC TTT TTG AGT CTC ACT CGG TTC AGC ACT GGT CTA GTT TTA
Gly Ser Lys Leu Phe Leu Ser Leu Thr Arg Phe Ser Thr Gly Leu Val Leu

4450          4460          4470          4480          4490          4500
GGA AAC ATG ACT ATT GAC AGC AAT GCA TCC TTT GGG CAA TAC ATT AAC GCG
Gly Asn Met Thr Ile Asp Ser Asn Ala Ser Phe Gly Gln Tyr Ile Asn Ala

          4510          4520          4530          4540          4550
GGA CAC GAA CAG ATC GAA TGC TTT ATA TTG TTG GAC AAT CAG GGT AAC CTA
Gly His Glu Gln Ile Glu Cys Phe Ile Leu Leu Asp Asn Gln Gly Asn Leu

        4560          4570          4580          4590          4600
AAA GAA GGA TCT AAC TTG CAA GGC ACT TGG GAA GTG AAG AAC AAC CCC TCT
Lys Glu Gly Ser Asn Leu Gln Gly Thr Trp Glu Val Lys Asn Asn Pro Ser

      4610          4620          4630          4640          4650
GCT TCC AAA GCT GCT TTT TTG CCT TCC ACC GCC CTA TAC CCC ATC CTC AAC
Ala Ser Lys Ala Ala Phe Leu Pro Ser Thr Ala Leu Tyr Pro Ile Leu Asn
```

FIG. 7P

```
     4660          4670          4680          4690          4700
GAA AGC CGA GGG AGT CTT CCT GGA AAA AAT CTT GTG GGC ATG CAA GCC ATA
Glu Ser Arg Gly Ser Leu Pro Gly Lys Asn Leu Val Gly Met Gln Ala Ile

   4710          4720          4730          4740          4750
CTG GGA GGC GGG GGC ACT TGC ACT GTG ATA GCC ACC CTC AAT GGC AGA CGC
Leu Gly Gly Gly Gly Thr Cys Thr Val Ile Ala Thr Leu Asn Gly Arg Arg

  4760          4770          4780          4790          4800
AGC AAC AAC TAT CCC GCG GGC CAG TCC ATA ATT TTC GTG TGG CAA GAA TTC
Ser Asn Asn Tyr Pro Ala Gly Gln Ser Ile Ile Phe Val Trp Gln Glu Phe

 4810          4820          4830          4840          4850
AAC ACC ATA GCC CGC CAA CCT CTG AAC CAC TCT ACA CTT ACT TTT TCT TAC
Asn Thr Ile Ala Arg Gln Pro Leu Asn His Ser Thr Leu Thr Phe Ser Tyr

4860          4870          4880          4890          4900
TGG ACT TA AAT AAG TTG GAA ATA AAG AGT TAA ACT GAA TGT TTA AGT GCA
Trp Thr

4910          4920          4930          4940          4950
ACA GAC TTT TAT TGG TTT TGG CTC ACA ACA AAT TAC AAC AGC ATA GAC AAG

4960          4970          4980          4990          5000
TCA TAC CGG TCA AAC AAC ACA GGC TCT CGA AAA CGG GCT AAC CGC TCC AAG
```

FIG. 7Q

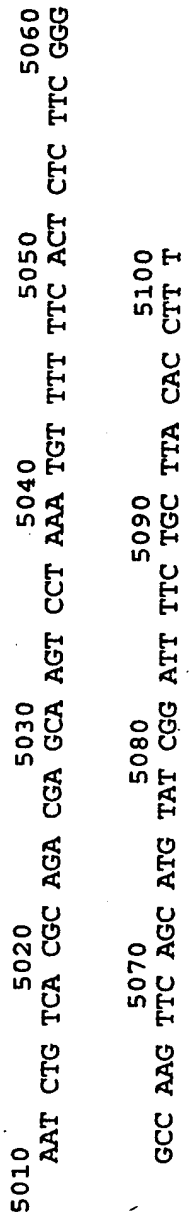

5010
AAT CTG TCA CGC AGA CGA GCA AGT CCT AAA TGT TTT TTC ACT CTC TTC GGG
5020
5030
5040
5050
5060
GCC AAG TTC AGC ATG TAT CGG ATT TTC TGC TTA CAC CTT T
5070
5080
5090
5100

FIG. 7R

```
Ad2     MSKEIPTPYMWSYQPQMGLAAGAAQDYSTRINYMSAGPHMISRVNGIRAH   50
BAV3        LIKQPVVGTTHV----------------------EMPRNEVLEQH   23
Ad2     RNRILLEQAAITTTPRNNLNPRSWPAALVYQESPAPTTVVLPRDAQAEVQ  100
BAV3    LTSHGAQIAGGG-----AAGDYFKSPTSARTLIPLTASCL------RPDG   62
Ad2     MTNSGAQLAGGFRHRVRSPGQGITHLKIRGRGIQLNDESVSSSLGLRPDG  150
BAV3    VFQLGGGSRSSFNPLQTDFAFHALPSRPRHGGIGSRQFVEEFVPAVYLNP  112
Ad2     TFQIGGAGRSSFTPRQAILTLQTSSSEPRSGGIGTLQFIEEFVPSVYFNP  200
BAV3    YSGPPDSYPDQFIRHYNVYSNSVSGYS  139
Ad2     FSGPPGHYPDQFIPNFDAVKDSADGYD  227
```

FIG. 8A

```
BAV3    M------EPDGVHAEQQFILNQISCANTALQRQREELASLVMLHACKRGL   77
Ad5     MTDTLDLEMDGIITEQRLL--ERRRAAAEQQRMNQELQDMVNLHQCKRGI   48
BAV3    FCPVKTYKLSLNASASEHSLHFEKSPSRFTLVNTHAGASVRVALHHQGAS  127
Ad5     FCLVKQAKVTYDSNTTGHRLSYKLPTKRQKLVVMVGEKPITITQHSVETE   98
BAV3    GSIRCSCSHAECLPVLLKTLCAFNFLD  154
Ad5     GCIHSPCQGPEDLCTLIKTLCGLKDLIPFN  128
```

FIG. 8B

```
BAV3    - MKRSVPQD--FNLVYPYKAKR-----PNIMPPFFDRNGFVENQEATLAML -43
          :::. : .  :: :::: .        : . :::   ::: :     :..
Ad2     - MKRARPSEDTFNPVYPYDTETGPPTVPFLTPPFVSPNGFQESPPGVLSLR -50

BAV3    - VEKPLTFDKE-GALTLGVGRGIRINPAGLLETNDLASAVFPPLASDEAGN -92
          :  ::  :   : :.: .: :. .  :: : .. ...
Ad2     - VSEPL--DTSHGMLALKMGSGLTLDKAGNLTSQNVTTV------------ -86

BAV3    - VTLNMSDGLYTKDNKLAVKVGPGLSLDSNNALQVHTGDGLTVTDDKVSLN -142
            .  :      ...     :.. .  :: : :   : ::   .:..
Ad2     - -----TQPLKKTKSNISLDTSAPLTI-TSGALTVATTAPLIVTSGALSVQ -130

BAV3    - TQAPLSTTSAGLSLLLGPSLHLGEEERLTVNTGAGLQISNNALAVKVGSG -192
          .:::::.                  . .:.. :   . .:   ::.   .
Ad2     - SQAPLT----------------VQDSKLSIATKGPITVSDGKLALQTSAP -164

BAV3    - ITVDAQNQLAASLGDGLESRDNKTVVKAGPGLTITNQALTVATGNGLQVN -242
          ..    :. .                .   :: :::  : .:
Ad2     - LSGSDSDTLTVT----------------------ASPPLTTATGS-LGIN -191

BAV3    - PEGQLQLNITAGQGLNFANNSLAVELGSGLHFPPGQNQVSLYPGDGIDIR -292
          :  . .:        :  . . .  :
Ad2     - MEDPIYVN----------NGKIGIKISGPLQVAQ---------------- -215

BAV3    - DNRVTVPAGPGLRMLNHQLAVASGDGLEVHSDTLRLKLSHGLTFENGAVR -342
                                    :::: .   :.: :. ..:
Ad2     - ----------------------------NSDTLTVVTGPGVTVEQNSLR -236
```

FIG. 8C-1

```
BAV3    - AKLGPGLGTDDSGRSVVRTGRGLRVANGQVQIFSGRGTAIGTDSSLTLNI -392
Ad2     - TKVAGAIGYDSSNNMEIKTGGGMRINNNL--LILDVDYPFDAQTKLRLKL -284

BAV3    - RAPLQFSGPALTASLQGSGPITYNSNNGTFGLSIGPGMWVDQNRLQVNPG -442
Ad2     - ----------------GQGPLYINASHN----------------LDINYN -302

BAV3    - AGLVFQGNNLVPNLADPLAISDSKISLSLGPGLTQASNALTLSLGNGLEF -492
Ad2     - RGLYL--------------FNASNNTKKLEVSIKKSS---------GLNF -329

BAV3    - SNQAVAIKAGRGLRFESSSQALESSLTVGNGLTLTDTVIRPNLGDGLEVR -542
Ad2     - DNTAIAINAGKGLEFDTNT------------------------------- -348

BAV3    - DNKIIVKLGANLRFENGAVTAGTVNPSAPEAPPTLTAEPPLRASNSHLQL -592
Ad2     - ------------------------------------------------- -348

BAV3    - SLSEGLVVHNNALALQLGDGMEVNQHGLTLRVGSGLQMRDGILTVTPSGT -642
Ad2     - ----------------SESPDIN--PIKTKIGSGID-------YNENGA -372

BAV3    - PIEPRLTAPLTQTENGIGLALGAGLELDESALQVKVGPGMRLNPVEKYVT -692
Ad2     - MIT----------------KLGAGLSFDNSG------------------- -387
```

FIG. 8C-2

```
BAV3    - LLLGPGLSFGQPANRTNYDVRVSVEPPMVFGQRGQLTFLVGHGLHIQNSK -742
Ad2     - -----AITIG-----NKNDDKLTLWTTPDPSP--------------NCR -412

BAV3    - LQLNLGQGLRTDPVTNQLEVPLGQGLEIADESQVRVKLGDGLQFDSQARI -792
Ad2     - IHSD------------------------NDCKFTLVLT---KCGSQVLA -434

BAV3    - TTAPNMVTETLWTGTGSNANVTWRGYTAPGSKLFLSLTRFSTGLVLGNMT -842
Ad2     - TVAALAVSGDLSSMTGTVASVS----------IFLRFDQ--NGVLMENSS -472

BAV3    - IDSNASFGQYINAGHEQIECFILLDNQGNLKEGSNLQGTWEVKNNPSASK -892
Ad2     - LKKHY----------------------WNFRNGNS------TNANPYTNA -494

BAV3    - AAFLPSTALYPILNESRGSLPGKNLVGMQAILGGGGTCTVIA-TLNGRRS -941
Ad2     - VGFMPNLLAYP---KTQSQTAKNNIVSQVYLHGDKTKPMILTITLNGTSE -541

BAV3    - NNYPAGQSII---FVWQ-EFNTIARQPLNHSTLTFSYWT -976
Ad2     - STETSEVSTYSMSFTWSWESGKYTTETFATNSYTFSYIAQE -582
```

FIG. 8C-3

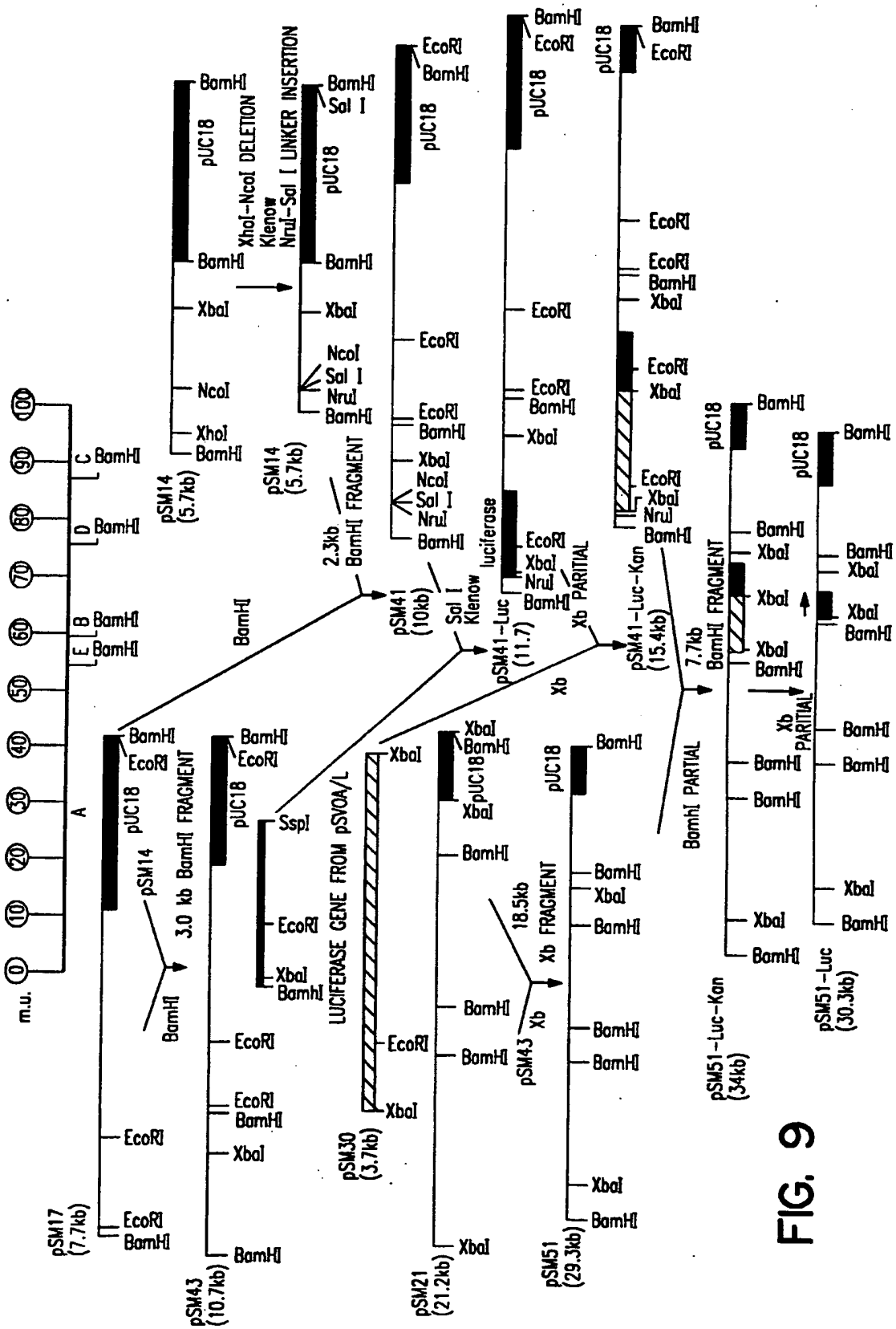
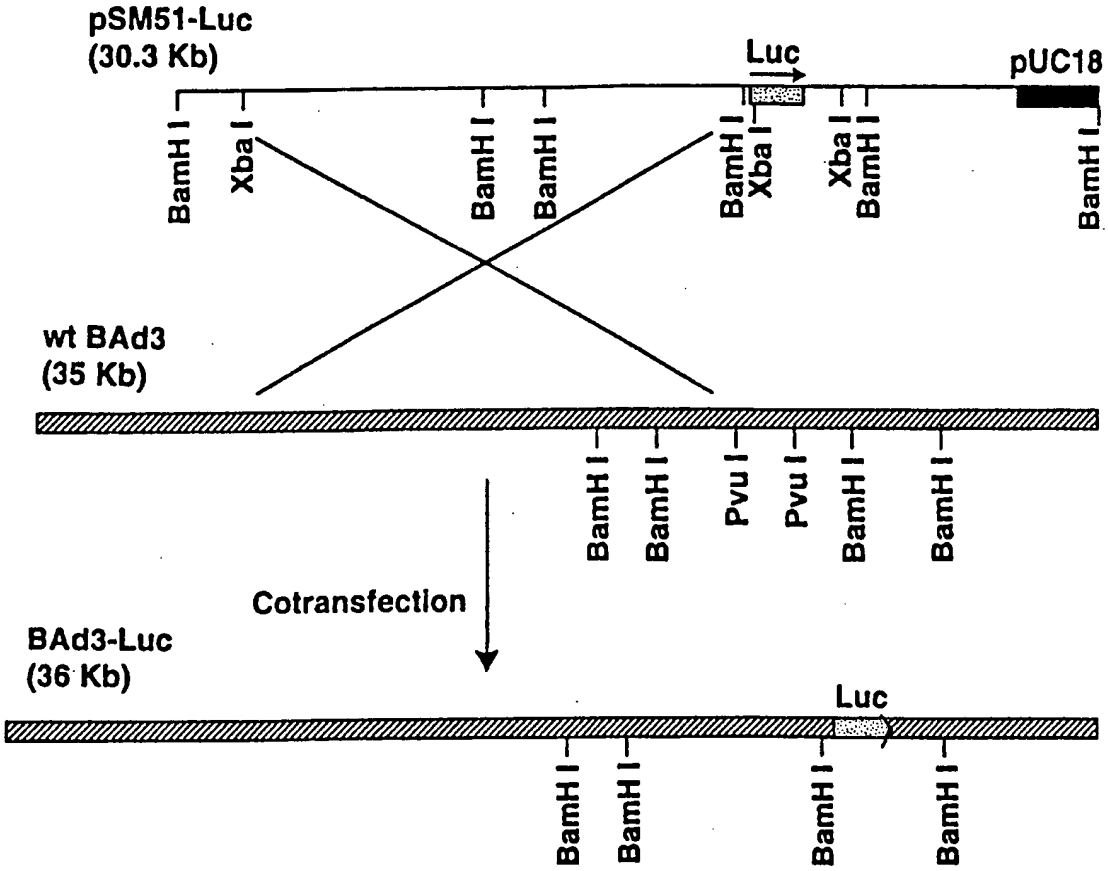

m.u.
A
B
C
D
E
pSM17 (7.7kb)
pSM14 (5.7kb)
3.0 kb BamHI FRAGMENT
pSM43 (10.7kb)
pSM14 (5.7kb)
XhoI-NcoI DELETION
Klenow
NruI-SalI LINKER INSERTION
2.3kb BamHI FRAGMENT
pSM41 (10kb)
LUCIFERASE GENE FROM pSVOA/L
pSM30 (3.7kb)
pSM21 (21.2kb)
pSM41-Luc (11.7)
luciferase
pSM41-Luc-Kan (15.4kb)
18.5kb Xb FRAGMENT
pSM43
pSM51 (29.3kb)
7.7kb BamHI FRAGMENT
pSM51-Luc-Kan (34kb)
pSM51-Luc (30.3kb)
pUC18
BamHI
EcoRI
XbaI
NcoI
SalI
NruI
XhoI
SspI
XbaI
PARTIAL
Xb

FIG. 9


pSM51-Luc
(30.3 Kb)
Luc
pUC18
BamH I
Xba I
BamH I
BamH I
BamH I
Xba I
Xba I
BamH I
BamH I
wt BAd3
(35 Kb)
BamH I
BamH I
Pvu I
Pvu I
BamH I
BamH I
Cotransfection
BAd3-Luc
(36 Kb)
Luc
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BamH I
BamH I
BamH I

FIG. 10

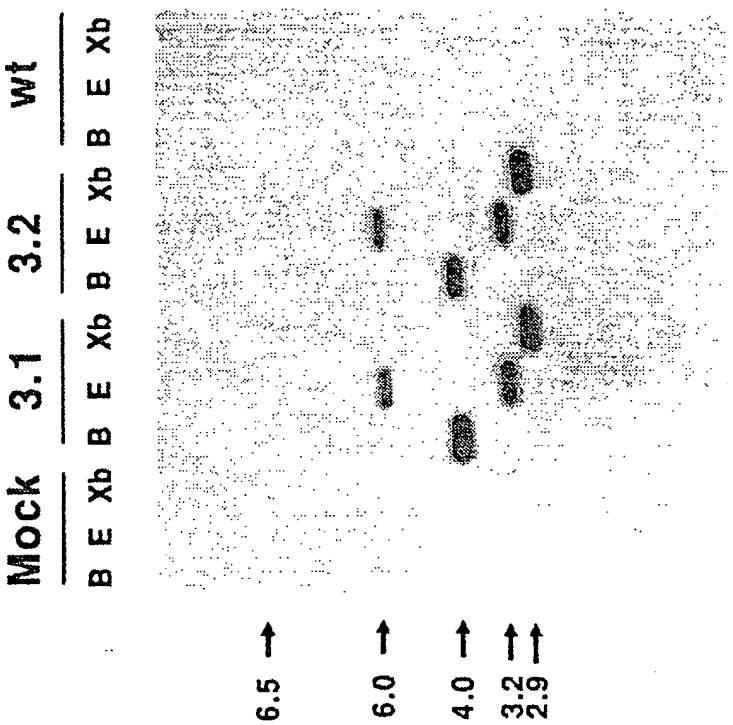


FIG. IIB

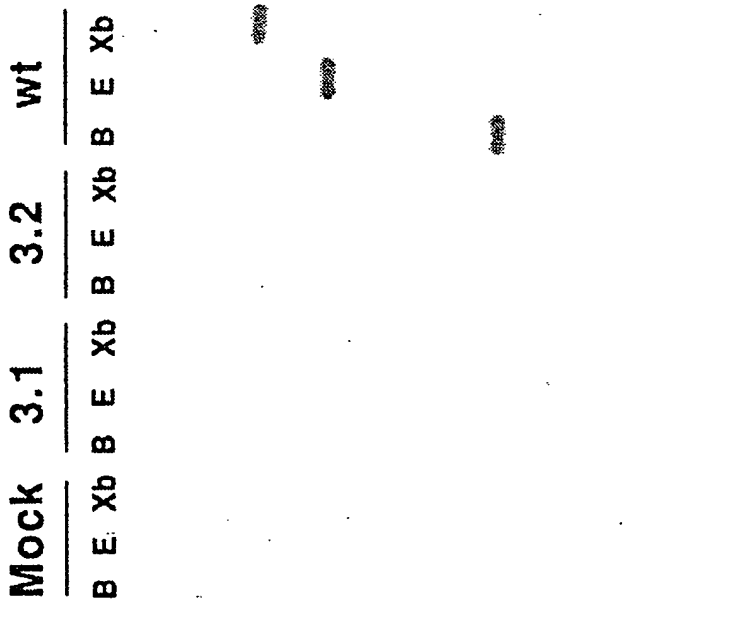


FIG. IIA

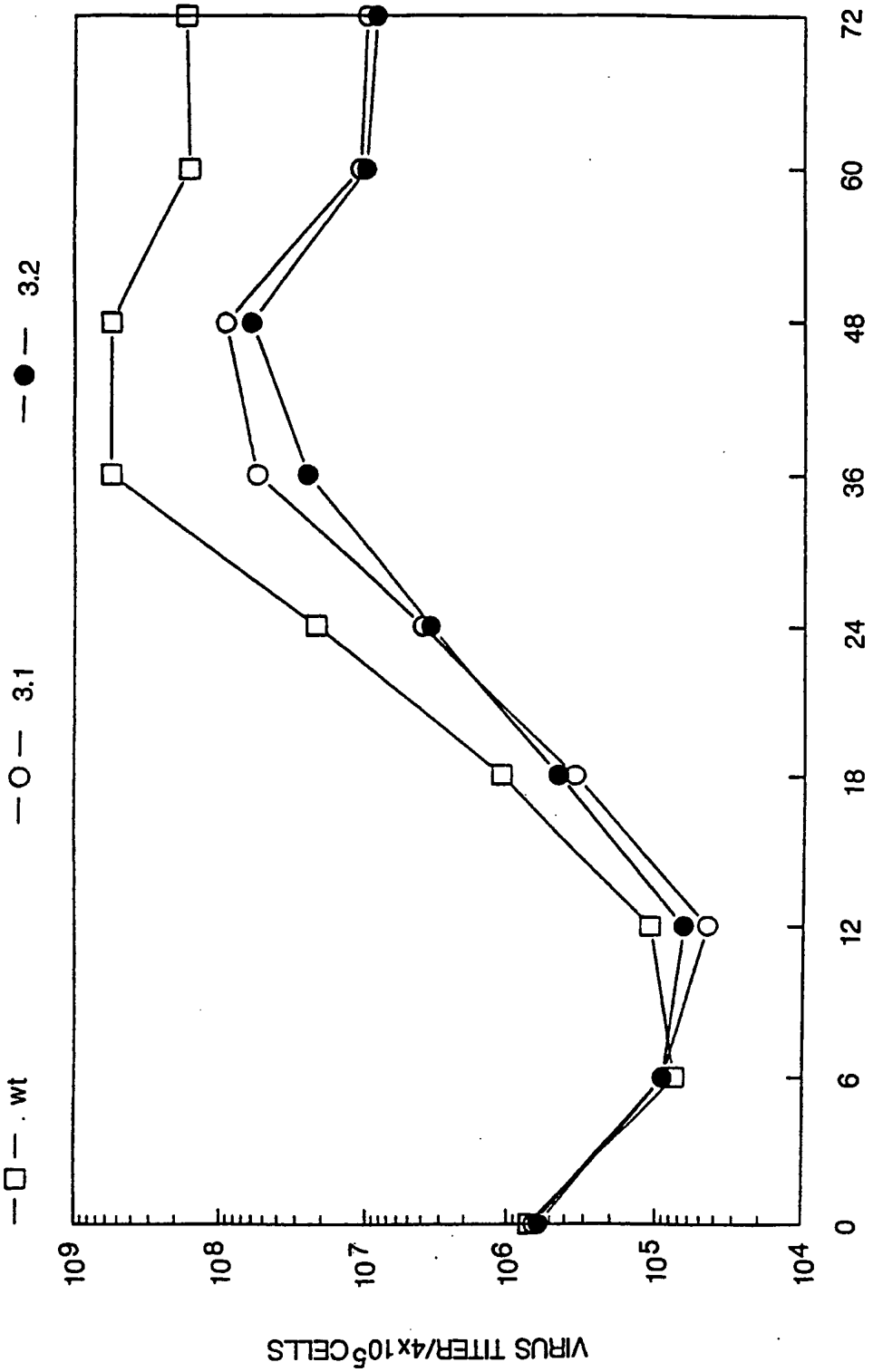

—□— wt
—○— 3.1
—●— 3.2
VIRUS TITER/4x10⁵CELLS
10⁹
10⁸
10⁷
10⁶
10⁵
10⁴
0
6
12
18
24
36
48
60
72
HOURS POST-INFECTION

FIG. 12

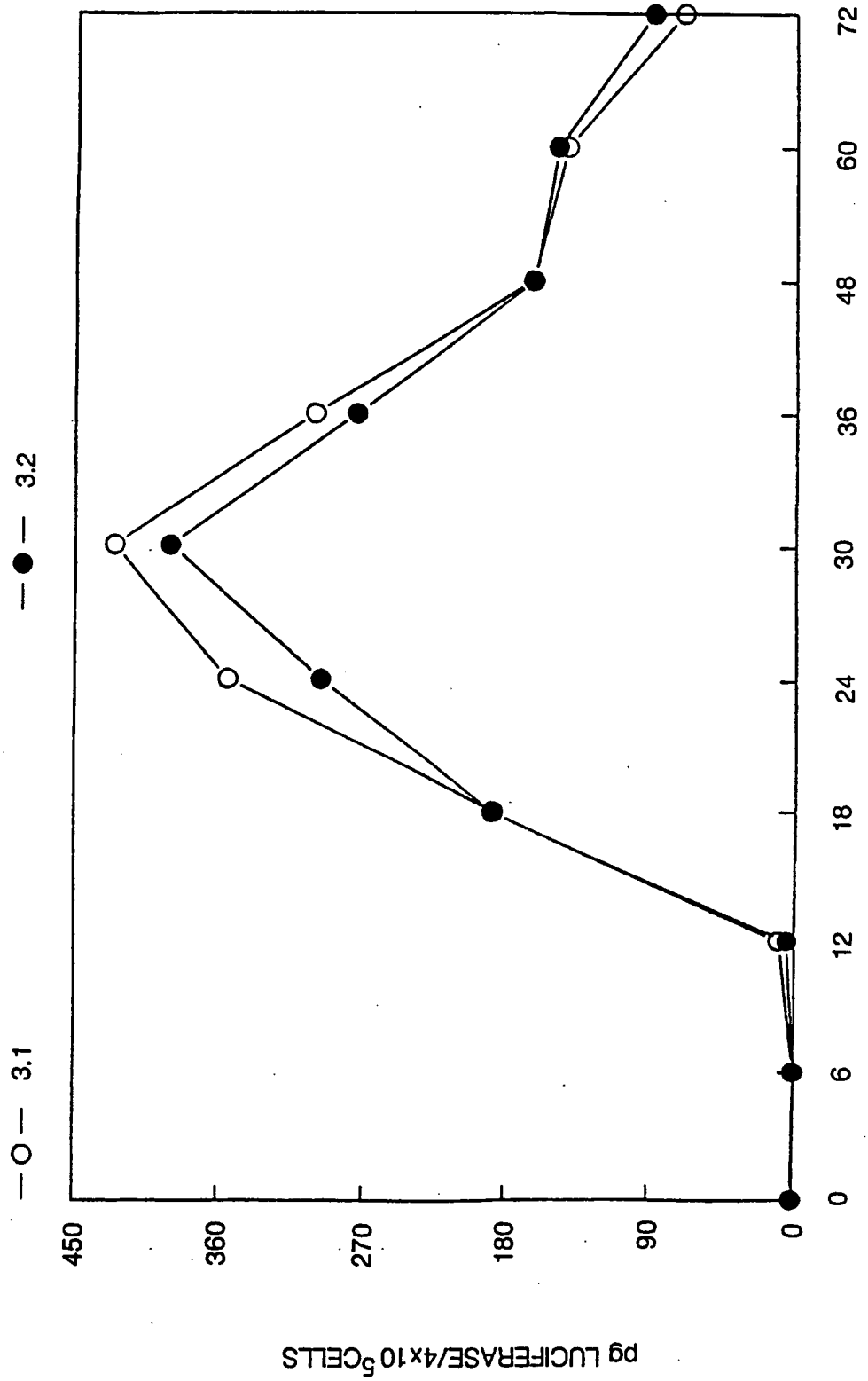

—O— 3.1
—●— 3.2
450
360
270
180
90
0
0
6
12
18
24
30
36
48
60
72
HOURS POST-INFECTION
pg LUCIFERASE/4x10⁵CELLS

FIG. 13

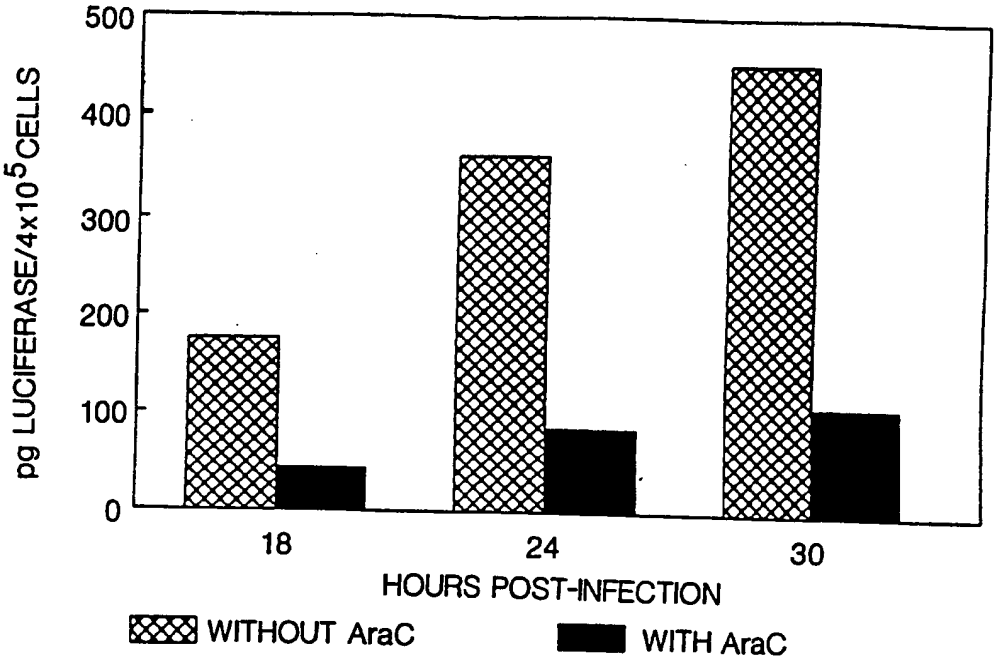


FIG. 14A

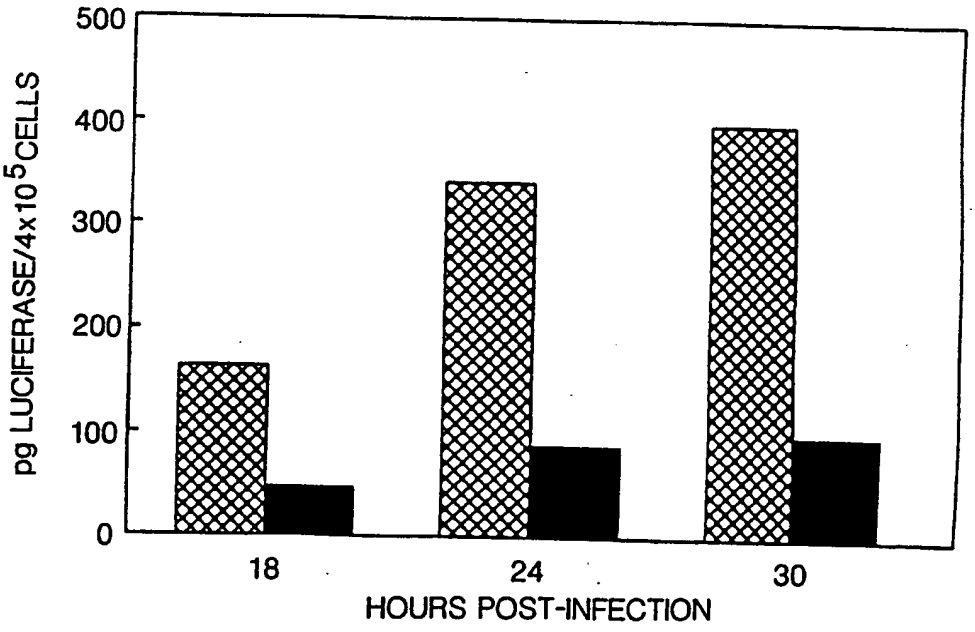


FIG. 14B

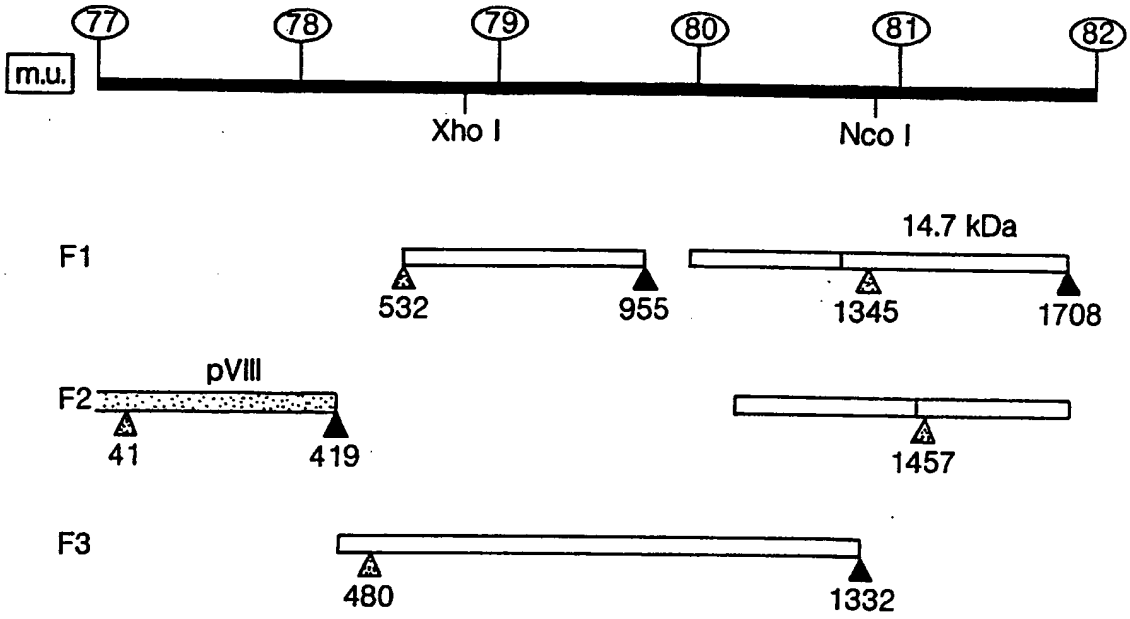


FIG. 15A

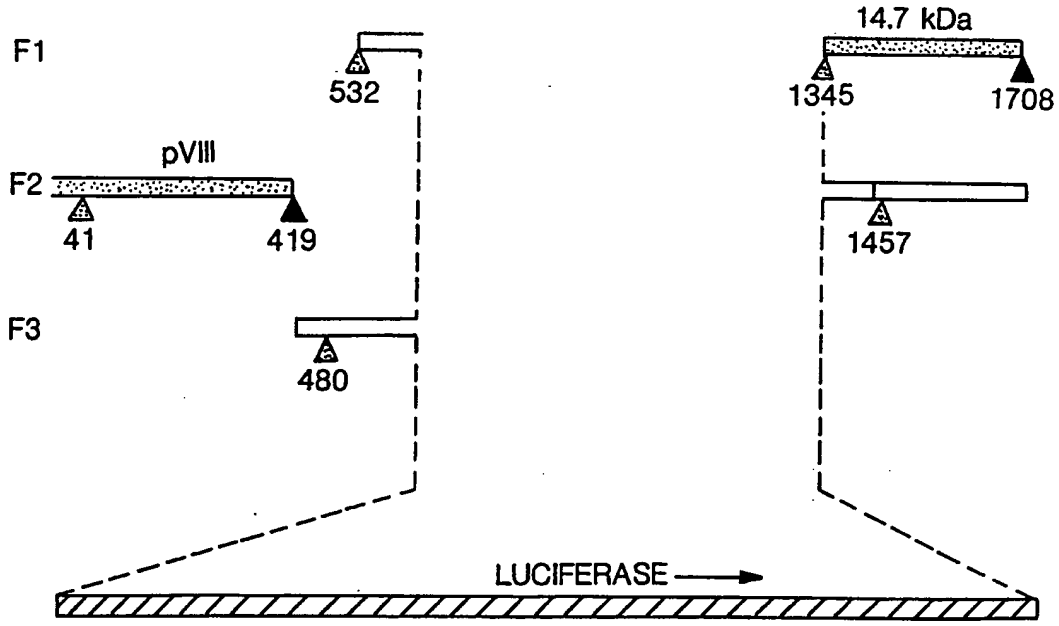


FIG. 15B

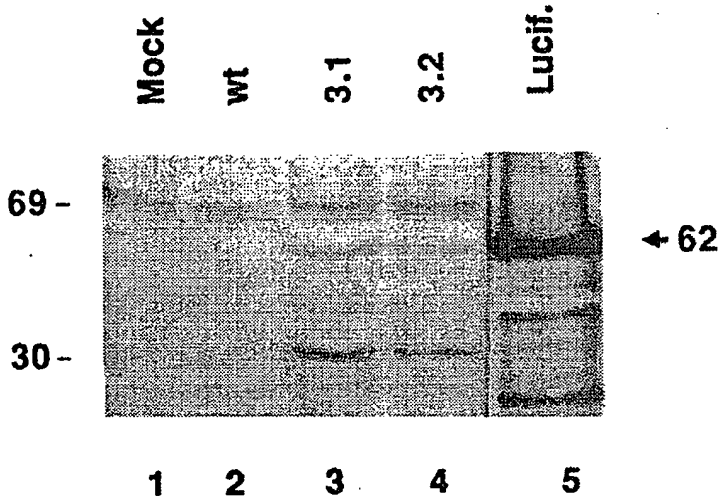
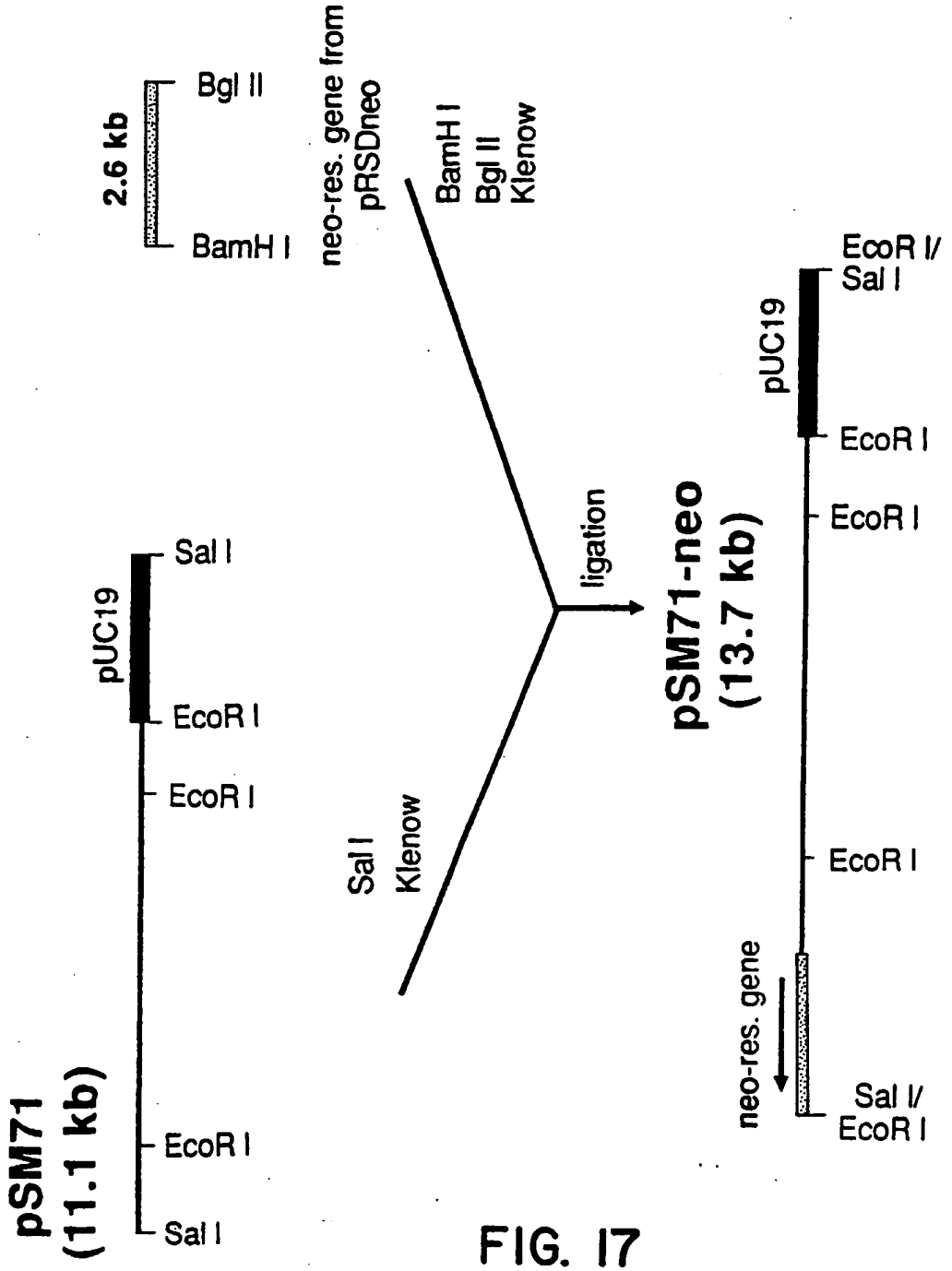


FIG. 16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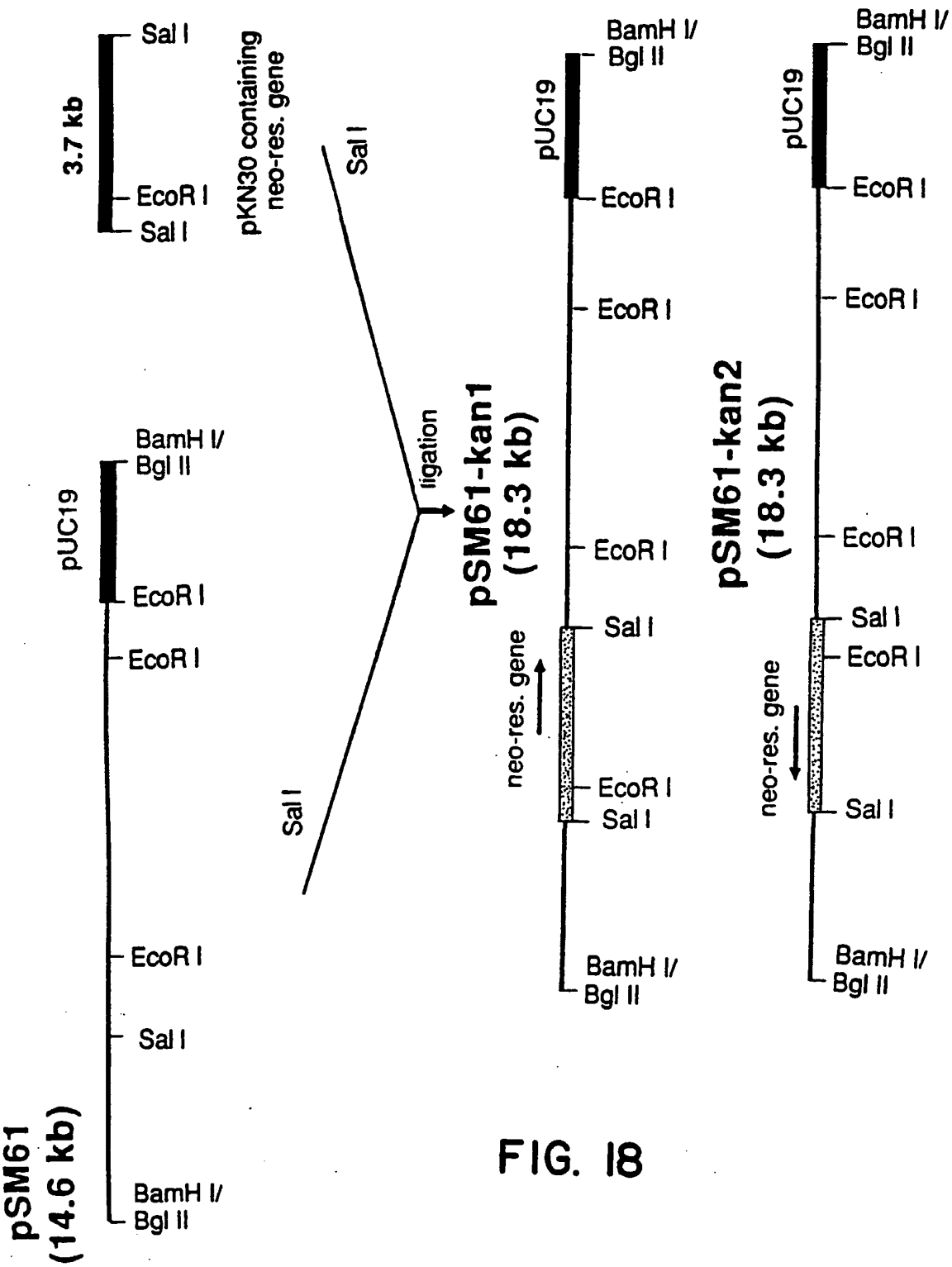
Bgl II
BamH I
neo-res. gene from pRSDneo
BamH I
Bgl II
Klenow
EcoR I/
Sal I
pUC19
EcoR I
EcoR I
pSM71-neo
(13.7 kb)
ligation
Sal I
pUC19
EcoR I
EcoR I
Sal I
Klenow
EcoR I
neo-res. gene
Sal I/
EcoR I
pSM71
(11.1 kb)
EcoR I
Sal I

FIG. 17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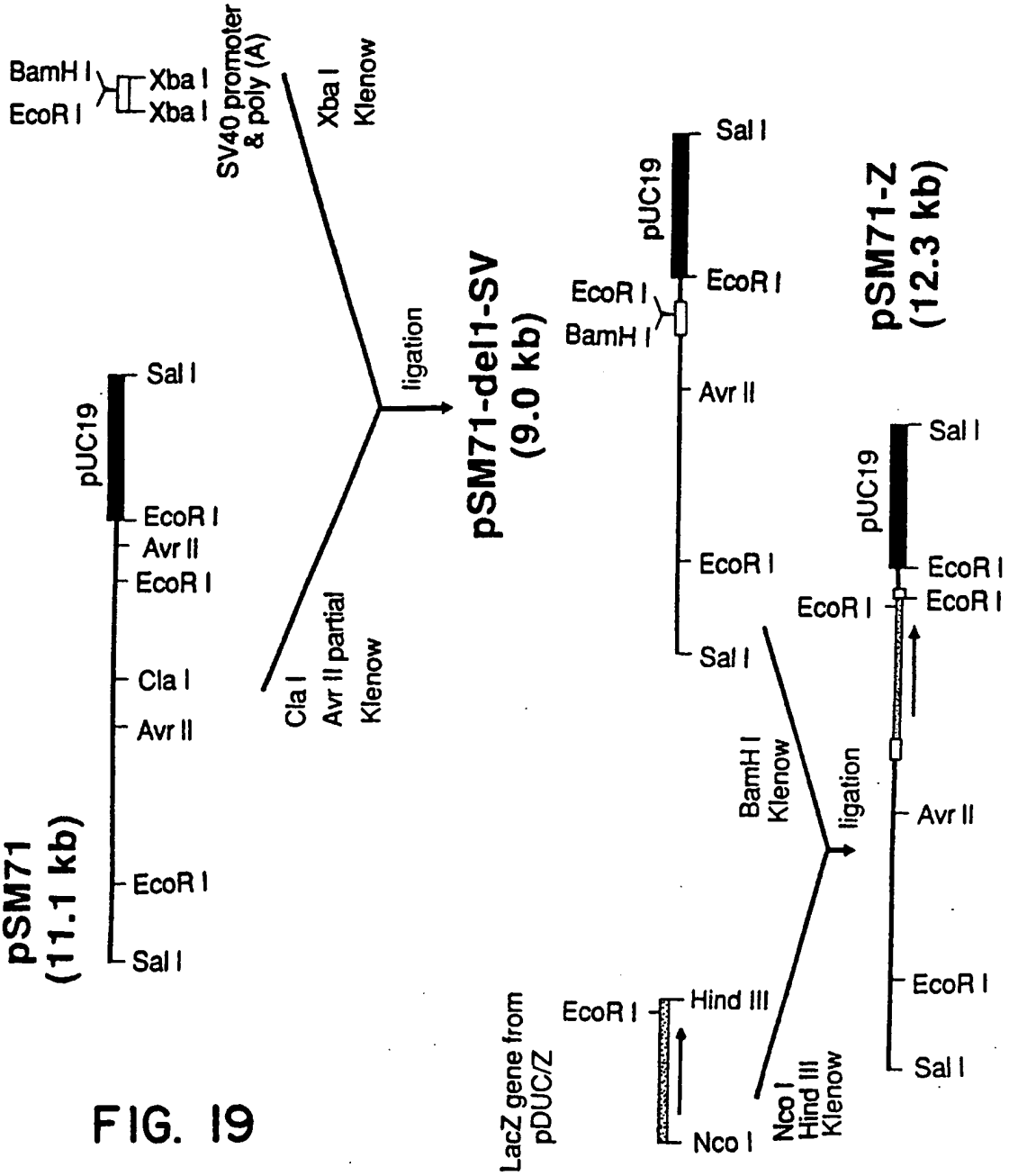
3.7 kb
EcoR I
Sal I
pKN30 containing neo-res. gene
Sal I
ligation
Sal I
BamH I/ Bgl II
pUC19
EcoR I
EcoR I
pSM61 (14.6 kb)
EcoR I
Sal I
BamH I/ Bgl II
pUC19
BamH I/ Bgl II
EcoR I
EcoR I
pSM61-kan1 (18.3 kb)
EcoR I
Sal I
neo-res. gene
EcoR I
Sal I
BamH I/ Bgl II
pUC19
BamH I/ Bgl II
EcoR I
EcoR I
pSM61-kan2 (18.3 kb)
EcoR I
Sal I
EcoR I
neo-res. gene
Sal I
BamH I/ Bgl II

FIG. 18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EcoR I
Xba I
Xba I
SV40 promoter & poly (A)
Xba I
Klenow
ligation
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Cla I
Avr II partial
Klenow
pSM71 (11.1 kb)
pUC19
Sal I
EcoR I
Avr II
EcoR I
Cla I
Avr II
EcoR I
Sal I
pUC19
Sal I
EcoR I
BamH I
Avr II
EcoR I
Sal I
BamH I Klenow
ligation
pSM71-Z (12.3 kb)
pUC19
Sal I
EcoR I
EcoR I
Avr II
EcoR I
Sal I
LacZ gene from pDUC/Z
EcoR I
Hind III
Nco I
Nco I Hind III Klenow

FIG. 19

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(30) Priority Data:
08/164,292 9 December 1993 (09.12.93) US

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(72) Inventors: MITTAL, Suresh, K.; #201-235 Kingsmere Boulevard, Saskatoon, Saskatchewan S7J 4J6 (CA). GRAHAM, Frank, L.; 34 Amelia Street, Hamilton, Ontario L8P 2V4 (CA). PREVEC, Ludvik; 944 LaSalle Park Road, Burlington, Ontario L7T 1M9 (CA). BABIUK, Lorne, A.; 245 East Place, Saskatoon, Saskatchewan S7J 2Y1 (CA).

(74) Agent: VAN ZANT, Joan, M.; Scott & Aylen, 60 Queen Street, Ottawa, Ontario K1P 5Y7 (CA).

(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

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With international search report.
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(54) Title: RECOMBINANT PROTEIN PRODUCTION IN BOVINE ADENOVIRUS EXPRESSION VECTOR SYSTEM

(57) Abstract

The present invention relates to novel live bovine adenovirus (BAV) expression vector systems in which part or all of one or both of the early region 1 (E1) and early region 3 (E3) genes are deleted and replaced by a foreign gene or fragment thereof and novel recombinant mammalian cell lines stably transformed with BAV E1 sequences, and therefore, express E1 gene products capable of allowing replication therein of a bovine adenovirus having an E1 deletion replaced by a heterologous nucleotide sequence encoding a foreign gene or fragment thereof and their use in production of (antigenic) polypeptides or fragments thereof for the purpose of live recombinant virus or subunit vaccine or for other therapies.

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FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/CA 94/00678

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/86 C12N5/10 A61K48/00 C12R1/92

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,A,4 920 209 (DAVIES ET AL.) 24 April 1990 *see the whole patent* ---	1-23
Y	JOURNAL OF VIROLOGY, vol. 57, no. 1, 1986 pages 267-274, Y. HAJ-AHMAD ET AL. 'Development of a helper-independent human adenovirus vector and its use in the transfer of HSV-tk gene' *see the whole article* ---	1-23
Y	Journal of cellular Biochemistry, UCLA symposium on Molecular and Cellular Biology, A.R. Liss, Inc. New York, 1988, Suppl. 12B, F109 *see the whole abstract* ---	1-23

-/--

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[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 July 1995	29.08.1995

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Marie, A

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JOURNAL OF GENERAL VIROLOGY, vol. 70, 1989 pages 429-434, L. PREVEC ET AL. 'Use of human adenovirus-based vectors for antigen expression in animals' *see the whole article* ---	1-23
Y	JOURNAL OF GENERAL VIROLOGY, vol. 73, 1992 pages 3295-3300, S.K. MITTAL ET AL. 'Sequence analysis of bovine adenovirus type 3 early region 3 and fibre protein genes' *see the whole article* ---	1-23
Y	JOURNAL OF VIROLOGY, vol. 49, no. 2, 1984 pages 604-608, S.-L. HU ET AL. 'Sequence homology between bovine and human adenoviruses' *see the whole article* -----	1-23

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCT/CA 94/00678

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-4920209	24-04-90	AU-B-	576907	08-09-88
		AU-A-	4884085	08-05-86
		CA-A-	1263305	28-11-89
		DE-A-	3586841	24-12-92
		EP-A,B	0181117	14-05-86
		GB-A,B	2166349	08-05-86
		IE-B-	58205	28-07-93
		JP-A-	61118326	05-06-86
		KR-B-	9312116	24-12-93